Clinics in Developmental Medicine

*Aicardi’s Diseases of the Nervous System in Childhood*
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Jean Aicardi (1926–2015)

Jean Aicardi, a clinician, clinical investigator and educator, left us on 3rd August 2015 at the age of 88.

Professor Aicardi had a passionate, life-long commitment to child neurology and clinical epileptology. He obtained his medical degree in 1955 at the Faculté de Médecine de Paris. He worked as a Research Fellow at the Harvard Medical School, headed the Pediatric Neurology Unit at the University Hospital Necker-Enfants Malades in Paris, was Director of Research at the French National Institute of Health and Medical Research INSERM (1986–1991) and was an Honorary Professor of Child Neurology at the Institute of Child Health, London UK (1992–1998).

Jean Aicardi was a pioneer in child neurology who contributed significantly to the description of several neurological entities including Aicardi syndrome in 1969; Aicardi-Goutières syndrome in 1984; Rett syndrome (together with Bengt Hagberg); alternating hemiplegia of childhood and others.


He was awarded several academic honors and distinctions including the Hower Award of the American Epilepsy Society (1986), the Epilepsy Research Award of the American Epilepsy Society (1995), the Ramon y Cajal Award, the International League Against Epilepsy-International Bureau for Epilepsy (ILAE-IBE) Ambassador for Epilepsy Award and the ILAE-IBE Life Achievement Award.

As a teacher Jean Aicardi believed in what he called the ‘members of the young generation’ and in 1999 he easily accepted the invitation to become the Founding Editor of an epilepsy journal devoted to electro-clinical semiology of the epilepsies, Epileptic Disorders, which today is the educational journal of the ILAE. At various times in his career, he was a member of the Editorial Boards of the journals Brain, Brain and Development, Epilepsia, Neuropediatrics, Pediatric Neurology and Journal of Child Neurology.

Jean Aicardi treated everyone with respect. He was always available and willing to provide thoughtful and humble advice to his colleagues and students, to the families that he deeply respected and the sick children he cared about so much. Aicardi had eight brothers and sisters, two of whom died in infancy and another of whom died in a German labour camp in 1945. He loved and respected his family. He was a loving husband and suffered enormously from the loss of his wife, Jeanne Couturier, in 2011.

A tireless clinician and teacher, ‘Monsieur Aicardi’ will be remembered not only as one of the founders of child neurology but also as the mentor of more than 100 child neurologists all...
over the world. His clinical ward rounds will remain unfor-
gettable to many of us. He was the one who taught us that ‘a major part of examination, and one too often neglected, consists of watching spontaneous activity of the child … the best manner of assessing CNS function and behaviour’. He strongly believed, and he was so right, that in this era of ubiquitous technology, careful observation of clinical signs and symptoms and their correct interpretation, based upon thorough knowledge, remain as essential as ever.

On a more personal note, allow me to thank my mentor and friend. He allowed me to share with him more than 30 years of teaching, discussions on differential diagnosis, on treatment, in writing papers and books. But above all, he shared with me important moments of our private lives. He was always present when I needed him. When the third edition of this book was published in 2009, I had just moved to Lyon to work on the development of a clinical epileptology and neurophysiology department. When he offered me a copy of his book Diseases of the Nervous System (3rd edn) he wrote on the cover page “… Our separation was finally not so hard for me to live with because I am so happy that you finally achieved what you always desired and merited …”

Some years later, when Jean asked me to take over the editor-ship of the 4th edition of this book, I was terrified but unable to say “No”. He helped me in selecting co-editors and authors (and this is an opportunity for me to thank them again). His wish was for the book to remain ‘resolutely clinical’.

Merci Monsieur!

ALEXIS ARZIMANOGLOU

REFERENCES

Jean Aicardi: A Brief Curriculum Vitae

• Born November 8th 1926
• Medical degree, Paris Faculty of Medicine (1955–1956)
• Research fellow, Harvard Medical School Boston, USA (1955–1956)
• Assistant Physician Hôpital des Enfants Malades, Paris, France (1957–1964)
• Assistant Physician Hôpital Saint-Vincent de Paul, Paris, France (1964–1979)
• Maître de Recherche, Institut National de la Santé et de la Recherche Médicale- INSERM (1969–1986)
• Director of Research INSERM and Head Pediatric Neurology Unit, University Hospital Necker-Enfants Malades, Paris, France (1986–1991)
• Visiting Scientist Miami Children’s Hospital, USA, 1993

MAIN ACADEMIC HONORS AND DISTINCTIONS

• Cornelia de Lange Medalion (Dutch Child Neurology Society)
• Fellow Royal College of Physicians (London)
• Honorary Fellow of the Royal College of Paediatrics and Child Health (London)
• Hower Award (US Child Neurology Society)
• Distinguished Investigator Award (Milken Award) (American Epilepsy Society)
• Honorary Member American Neurological Association
• Ambassador for Epilepsy (ILAE)
• Ramon y Cajal Award (Ibero-American Academy of Child Neurology)
• Peter Emil Becker Award (German Child Neurology society)

• Honoured Guest the XXth Cleveland Clinic Meeting Cleveland USA, 2002
• Honorary Member, European Paediatric Neurology Society, Göteborg, Sweden 2005
• President of the International Child Neurology Association (1990–1994)
• Légion d’Honneur (2009)

ACHIEVEMENTS

• Identified Aicardi’s syndrome in 1969
• Identified Aicardi-Goutières syndrome in 1984

PUBLICATIONS

• Epilepsy in Children. Lippincott, Williams and Wilkins, 1993
• Aicardi’s Epilepsy in Children (with A Arzimanoglou, R Guerrini) Lippincott, Williams and Wilkins, 2003
• Founding Editor and Editor-in-Chief, Epileptic Disorders (1999–2004)
• 259 articles in international peer-reviewed journals
• 111 book chapters
About the Editors

Professor Alexis Arzimanoglou is the Director of the Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology at the University Hospitals of Lyon, France and Visiting Professor at the Universitat de Barcelona, Spain, coordinating the Epilepsy Research Program at the Hospital San Juan de Déu. He graduated from the Salonica University, Greece, trained in Neurology at Great Ormond Street Hospital, London, UK and at the Hôpital de la Salpetrière and in Child Neurology as a fellow of Jean Aicardi at the Hôpital des Enfants Malades in Paris, France. He then worked with Jean Aicardi for over 25 years. He served as Chair of the Scientific Committee of the European Paediatric Neurology Society; Editor-in-Chief of the International League Against Epilepsy (ILAE) educational journal Epileptic Disorders and Elected member of the European Commission of the ILAE. Together with Jean Aicardi and Renzo Guerrini he authored Aicardi’s Epilepsy in Children. He received the Ambassador for Epilepsy Award from the ILAE and the Aicardi Award for excellence in Paediatric Neurology from the EPNS. He is the editor of seven books and an author or co-author of nearly 150 scientific articles in the fields of cognition and medical and surgical treatment of childhood epilepsies.

Professor Anne O’Hare is Professor of Community Paediatrics and Director of the Salvesen Mindroom Centre for Learning Difficulties, at the University of Edinburgh. She is a developmental paediatrician with extensive clinical experience in neurodisability, neuroscience and child protection. Her research interests include how neurodevelopmental conditions impact on the development of speech, language, communication, motor skills and learning and the development of effective interventions.

Professor Michael V Johnston is a Professor of Neurology, Pediatrics and Physical Medicine and Rehabilitation at the Johns Hopkins University School of Medicine and the Chief Medical Officer and the Blum Moser Endowed Professor of Pediatric Neurology at the Kennedy Krieger Institute in Baltimore, Maryland, USA. He trained in paediatrics, neurology and neuroscience at Johns Hopkins University School of Medicine, and his clinical and research interests include fetal and neonatal neurology, as well as care for older children with cerebral palsy and neurogenetic disorders including Rett syndrome. He has been active in the development of strategies to protect the developing brain from hypoxic-ischaemic injury. He is one of the founding faculty members of the Neurosciences Intensive Care Nursery (NICN) research and clinical care group at Johns Hopkins Hospital, and he has also been a leader of the Phelps Cerebral Palsy Center at the Kennedy Krieger Institute.

Professor Robert Ouvrier is Emeritus Professor of child Neurology at the University of Sydney. After training in general paediatrics in Sydney, Perth and Papua-New Guinea, he undertook specialist training in child neurology at the Royal Children’s Hospital, Melbourne, the University of Kentucky (1969-70) and the Johns Hopkins Hospital, Baltimore USA (1971-72). He was then Head of the Department of Neurology at the Children’s Hospital at Westmead, Sydney for 25 years. In 1999, he became the Foundation Head of the Institute for Neuroscience and Muscle Research at The Children’s Hospital, Westmead. He was President of the International Child Neurology Association from 2006-2010. He is the author of two books, thirty book chapters and an author or co-author of over 150 scientific articles on paediatric neurology.
Authors’ Appointments

Alexis Arzimanoglou
Director of the Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology at the University Hospitals of Lyon, France; Visiting Professor at the Universitat de Barcelona, Spain

Nadia Bahi-Buisson
Professor in Paediatric Neurology, Necker Enfants Malades University Hospital, APHP; Paris Descartes – Sorbonne Paris Cité University, Imagine Institute; INSERM UMR-1163, Paris, France

Alasdair Bamford
Consultant, Paediatric Infectious Diseases, Great Ormond Street Hospital, London, UK

Karen Barlow
Paediatric Neurologist, Cumming School of Medicine, University of Calgary, Alberta, Canada

Peter Baxter
Consultant Paediatric Neurologist, Children’s Hospital Sheffield, UK

Nathalie Boddaert
Professor and Head of Department, Paediatric Radiology, Hôpital Necker Enfants Malades, Paris, France

Jaume Campistol-Plana
Professor and Head of the Department of Paediatric Neurology, Hospital San Juan de Déu Barcelona, Spain

Aabir Chakraborty
Consultant Paediatric Neurosurgeon, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Russell C Dale
Petre Associate Professor, Paediatric Neurology Research, Paediatrics and Child Health, Children’s Hospital, University of Sydney, Westmead, Australia

Bernard Dan
Professor of Neuroscience, Université libre de Bruxelles (ULB), Brussels; Director of Rehabilitation, Rehabilitation Hospital Inkendaal, Vlezenbeek, Belgium

Linda De Meirleir
Head of Paediatric Neurology and Metabolic Diseases and Medical Coordinator for Rare Disorders, Universitair Ziekenhuis (UZ) Brussel, Belgium

Linda S de Vries
Professor of Neonatal Neurology, Department of Neonatology, University Medical Centre Utrecht, the Netherlands

Gabrielle deVeber
Director, Children’s Stroke Program; Senior Scientist, Child Health Evaluation Sciences Program; Paediatric Neurologist, Division of Neurology, The Hospital for Sick Children (SickKids); Professor of Paediatrics, The Institute of Medical Science, University of Toronto, Toronto, Canada

Michael S Duchowny
Director, Neurology Training Programs, Nicklaus Children’s Hospital–Miami Children’s Health System; Professor of Neurology and Pediatrics, University of Miami Miller School of Medicine; Clinical Professor, Department of Neurology, Florida International University College of Medicine, Miami, Florida, USA

Adré J Du Plessis
Chief, Division of Fetal and Transitional Medicine; Director, Fetal Medicine Institute, Children’s National Medical Center, George Washington University School of Medicine, Washington DC, USA

Michael Eyre
Specialty Registrar in Paediatric Neurology, Great Ormond Street Hospital, London, UK

Emilio Fernandez-Alvarez
Professor, Neuropaediatric Department, Hospital Universitario San Juan de Dios, Barcelona, Spain

Robert Forsyth
Consultant Paediatric Neurologist, Great North Children’s Hospital; Senior Lecturer, Newcastle University, Newcastle, UK

Patricia Franco
Professor of Physiology; Coordinator of the Paediatric Sleep Unit at the Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology at the University Hospitals of Lyon & INSERM U1028, Lyon, France

Paddy Grattan-Smith
Clinical Associate Professor, Paediatrics and Child Health, Children’s Hospital, Westmead, Sydney, Australia

Richard Hayward
Professor of Paediatric Neurosurgery, Great Ormond Street Hospital, London, UK
Cheryl Hemingway  
Consultant Paediatric Neurologist, Great Ormond Street Hospital, London, UK

Michael V Johnston  
Chief Medical Officer and Blum Moser Endowed Chair for Pediatric Neurology, Kennedy Krieger Institute; Professor of Neurology, Pediatrics and Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Colin Kennedy  
Professor of Neurology and Paediatrics, University of Southampton; Honorary Consultant in Paediatric Neurology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Adam Kirton  
Professor of Paediatrics and Clinical Neuroscience, University of Calgary; Director of Calgary Paediatric Stroke Program, the Alberta Perinatal Stroke Project and the Alberta Children's Hospital Pediatric Non-Invasive Brain Stimulation Laboratory, Alberta, Canada

Ingeborg Krägeloh-Mann  
Professor of Paediatrics; Director Paediatric Neurology and Developmental Medicine, University Children's Hospital, Tübingen, Germany

Kenneth J Mack  
Professor of Child and Adolescent Neurology, The Mayo Clinic, Rochester, Minnesota, USA

Carey Matsuba  
Clinical Assistant Professor, Department of Opthalmology, University of British Columbia, Vancouver, Canada

Miriam Martinez-Biarge  
Neonatologist, Imperial College London, London, UK

Manoj Menezes  
Staff Specialist in Neurology, T.Y. Nelson Department of Neurology and Neurosurgery, The Children's Hospital at Westmead; Senior Clinical Lecturer, The University of Sydney, Australia

Robert Minns  
Emeritus Professor of Paediatric Neurology and Honorary Professorial Fellow, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK

Francesco Muntoni  
Professor, The Dubowitz Neuromuscular Centre, University College London, Institute of Child Health, London, UK

Kathryn N North  
Professor and Director of the Murdoch Children's Research Institute and the David Danks Professor of Child Health Research at the University of Melbourne, Australia

Anne O'Hare  
Professor of Community Paediatrics and Director of the Salvesen Mindroom Centre, University of Edinburgh, Edinburgh, UK

Robert Ouvrier  
Emeritus Professor of Paediatrics and Child Health, The Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney, Australia

Karine Pelc  
Consultant Paediatric Neurologist, Centre Hospitalier Universitaire Saint Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium

Eleni Panagiotakaki  
Senior Consultant, Department of Clinical Epileptology, Sleep Disorders and Functional Neurology in Children, Hôpital Femme Mère Enfant, University Hospitals of Lyon, Bron, France

Monique M Ryan  
Director, Department of Neurology, Royal Children's Hospital, Melbourne, Australia

Victoria San Antonio Arce  
Head of the Epilepsy, Sleep and Neurophysiology Section, Neurology Service, Sant Joan de Déu Barcelona Children's Hospital, Barcelona, Spain

Christian Sainte-Rose  
Université Paris Descartes and Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, Paediatric Neurosurgery Service, Paris, France

Mariacristina Scoto  
Specialty Doctor in Neuromuscular Diseases; Honorary Senior Clinical Research Associate, The Dubowitz Neuromuscular Unit, University College London; Institute of Child Health and Great Ormond Street Hospital, London, UK

Bruce K Shapiro  
Professor of Pediatrics, The Johns Hopkins University School of Medicine, Vice President, Training, Kennedy Krieger Institute, Baltimore, USA

Marc Tardieu  
Professor of Pediatrics, Neurology, Université Paris Sud; Head, Immunology of Viral and Autoimmune Diseases, Inserm U1184, Paris, France

Roberto Tuchman  
Chief, Department of Neurology, Nicklaus Children's Hospital, Miami Children's Health System, Miami, USA

Dominic NP Thompson  
Consultant Paediatric Neurosurgeon, Department of Neurosurgery, Great Ormond Street Hospital, London, UK

David Walker  
Professor of Paediatric Oncology, Children's Brain Tumour Research Centre, University of Nottingham, Nottingham, UK

Andrew Whitelaw  
Emeritus Professor of Neonatal Medicine, University of Bristol, Bristol, UK
Preface to Third Edition

Diseases of the nervous system in infancy and childhood have a profound impact on the life of patients and their families and are probably the most disruptive of all pediatric ailments. Around 20–30% of hospitalized pediatric patients have a neurological problem, either as a sole or as an associated complaint. However, many well-educated pediatricians not infrequently feel uncomfortable and hesitant about how to treat children and what to tell to parents of patients with neurological disorders.

Diseases of the Nervous System in Childhood is meant for physicians with an interest in pediatric neurological diseases, whether pediatricians, neurologists, child neurologists or physi-cians dedicated to developmental medicine, and deals only with diseases of the nervous system (as indicated by its title). It is res-olutely clinically oriented but, when necessary, some notions concerning pathogenesis and mechanisms are provided.

This third edition has been extensively updated to cover the tremendous volume of new information collected over the past 10 years, while trying to maintain the size of the book within reasonable limits. In spite of considerable efforts the speed of acquisition of new information is such that no textbook can pretend to be really up to date with respect to the very latest data. Electronic databases fulfil the need for ‘last minute’ results, but in a fragmentary and often uncritical manner. Books, on the other hand, aim to give a different, more global and balanced overview of a subject, taking into account the relative importance of the various parts, and assessing and selecting the material in the light of the experience of authors. I believe this synthetic and critical process is more essential than ever in view of the abundance of the material available.

The rapid increase of new data necessitated some rearrangements of this book. Unlike in the earlier editions where I had principally edited all the chapters, I felt this was no longer possible and invited Dr Martin Bax and Professor Chris-topher Gillberg to be co-editors with me, and they viewed all the ma-terial. In addition, whereas previously I had taken responsibility for the majority of chapters, we decided it was necessary to invite more collaborators to author certain chapters. We are very grateful to those who have given their time and knowledge for the completion of the book.

As before we have not included a chapter on the neurological examination of infants and children. Excellent books and mono-graphs on these topics are available (e.g. Cioni and Mercuri 2008). We have also omitted the chapter on fetal neurology as this highly specialized area of pediatric neurology is also well covered by a number of texts (e.g. Hill and Volpe 1989, Levene et al. 2001).

I wish to introduce this book with a few remarks, based on a 40-year experience, on what could be termed the ‘phi-losophy’ of pediatric neurological examination. In this age of ubiquitous technology, I strongly believe that collection of clinical data and their correct interpretation remain as essential as ever.

In the first place, the eminent importance of history taking needs to be re-emphasized, as the history of the disease – as well as that of the child from conception and that of his/her family–forms the initial and most important step of the diagnosti-c approach. For most conditions, the diagnosis is estab-lished by thorough clinical history even before, and much more frequently than by, examination (Dooley et al. 2003). History taking is a dif-ficult art requiring careful listening, patience, clinical acumen and understanding. It also necessi-tates a thorough knowledge of which information is worth looking for, and constant attention to possibly revealing words that may occasionally emerge out of a casual or even apparently irrelevant conversation.

This emphasis on history taking does not in any way min-imize the essentiality of neurological examination, which should be as thorough as possible and largely guided by histori-cal data. However, in children, and especially in infants or neonates, it cannot be conducted systematically as in adults. Attempts at ‘adult-type’ examination will lead to crying and fussing. Much of the examination should not require that the child be lying, as the lying position will often frighten the child by reminding him/her of previous unpleasant experiences and prevent the gathering of more important information on central nervous system functioning. After all, the vertical posture has been a major evolutionary acquisition and, since the emer-gence of Homo erectus, most human activities take place in the standing position.

Indeed, a major part of examination, and one too often ne-glected, consists of watching the spontaneous activity of the child. While an early example of observation is of neo-natal and early infantile general movements, which have been shown to have predictive value (Ferrari et al. 1990, Einspieler and Prechtl 2005), later observation should be watching children’s sponta-neous activity with special emphasis on how they relate to their surroundings and to other children or adults, the duration of their capacity of attention, and their...
verbal or preverbal communica-tion. Playing or interacting
with the child is the best manner of assessing CNS function
and provides information not only on purely neurological
function but also on behav-ioural problems, which is clearly
essential for the diagnosis of the behavioural syndromes that
are currently taking a major place in child pathology. Adva-
antage can be taken as often as possible of video-recording for
prolonged observation of children's behaviour and is also par-
ticularly useful for the precise study of transient events such as
seizures as it allows leisurely and repeated analysis of the ictal
phenomena.

It cannot be overemphasized that the basic role of the ner-
vous system is to produce not just reflexes but above all com-
plex and adaptive behaviours that are much more informative
on the status of the central nervous system than elementary
responses to imposed stimuli. This is best achieved by pro-
longed observa-tion of the qualitative aspects of the sponta-
neous activities of the children or infants. All too often, the
child is examined but not looked at.

Spectacular advances in medical technologies made
over the past decades have revolutionized and enormously
increased our diagnostic possibilities, both pre- and postna-
tally (and recently even in pre-implantation diagnosis), and
also improved follow-up surveillance far beyond what could
be imagined 20 years ago. Neuroimaging, especially MRI,
has become an almost rou-tine investigation, and with con-
tinuing improvements and new developments such as diffu-
sion-weighted MRI, tensor tractog-raphy, functional MRI
and MR spectrography can now provide information not
only on the anatomy but also on the function of some of the
central nervous system structures. Biochemical progress in the
molecular structure of proteins and the advent of molecular
genetics allow a precise diagnosis of many genetic dis-or-
derws even in the absence of clinical manifestations, represent-ing
an entirely new field opening new perspectives in diagnosis
and prevention. However, at the same time, the availability
of these multiple techniques has made the task of choosing
among the possibilities offered much more difficult. Investiga-
tions should not be performed indiscriminately or systemati-
cally but only after formulation of one (or a limited number)
of diagnos-tic hypotheses, arising mainly from history and
clinical findings, with a view to validate or reject them on the
basis of their con-frontation by clinical and laboratory data.
Clinical medicine is and must remain an intellectual process
whereby all sources of information, whether clinical stricto
sensu or arising from tech-nical aids, are used to formulate a
diagnosis that will lead to the best possible care of the patient.
One's last task is to communi-cate and discuss our, some-
times complex, findings with the pa-tient and their family. I
hope this new edition of Diseases of the Nervous System in
Childhood will help the clinician to carry out his/her tasks
effectively.

JEAN AICARDI
Paris, September 2008

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movements in preterm infants with brain lesions. Early Hum


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natal Neurology and Neurosurgery. 3rd edn. London: Churchill
Livingstone.
Preface to Fourth Edition

Jean Aicardi (1926–2015) authored the first edition of Diseases of the Nervous System in Childhood, which was published in 1992. Professor Aicardi was one of the most insightful clinicians of his time, who had witnessed the birth of child neurology as an entirely new field of medicine. His book rapidly became a premier reference tool for those clinicians around the world who were fascinated by the highly complex field of study – the developing nervous system.

Only six years later in his preface to the second edition (1998), Aicardi wrote “… the pace of progress both in medicine and in communication techniques has been so fast in the past few years that there are those who wonder whether books are still useful. They argue that new data are accumulating so rapidly that only computerized databases and networks can permit users to keep abreast of current developments in basic and clinical sciences, and that books are irredeemably condemned to be outdated even at the time of publication”.

A third edition followed in 2009 because, as Aicardi was already arguing in 1998, “… immediate availability of such an overwhelming volume of information may be a mixed blessing as assessment of the quality and relevance is left to the judgement of each user, whereas books may be of some help in soliciting the most important data and giving an idea of their organization and significance, assuming that the author’s choices are backed by a certain experience and provided they are not excessively biased”.

As Editors of the fourth edition our first challenge was to respect, and as much as possible reproduce, the resolutely clinical orientation of the previous editions. All authors were free either to update the chapters or completely rewrite them, under one condition, that, as Aicardi did, they target the clinical readers. As with the previous editions they were asked to contribute to a reference book for practising child neurologists that would also provide a comprehensive overview for those training in child neurology.

We are happy to acknowledge that, in this era of genomic medicine, all authors respected the fact that understanding the phenotypic spectrum of the huge variety of disorders of the child’s nervous system remains of paramount importance. Family history-taking needs to be taught to all those who wish to practise child neurology. A thorough clinical and physical examination is the second indispensable step towards diagnosis.

The combination of these two steps represents the optimal road to the formulation of a diagnostic hypothesis, then followed by the selection of the most appropriate laboratory and/or imaging investigations and the correct interpretation of the impressive quantity of complex results provided by all types of screening.

The structure of the book was globally respected, but some important changes have been implemented in this fourth edition. The chapter on Fetal Neurology (missing from the third edition) has been reintroduced. Movement disorders, previously discussed in different chapters, are now treated in a dedicated section to better reflect recent advances in the field. Some of the paroxysmal disorders other than epilepsy have also been treated separately and the section on developmental and neuropsychiatric disorders has been modified.

We also respected the wish of Aicardi and deliberately did not include a specific section on the neurological examination of infants and children at various ages or give data on maturation of the nervous system. There are already Excellent books and monographs on these topics.

We are also conscious of the fact that almost unavoidably (considering where nearly all authors and editors were located) the book mainly focuses on child neurology in high-income countries. However, we believe that by respecting the clinical approach, as Aicardi did, a large part of the content will also be useful to those colleagues working in countries where technical facilities are not optimal or may be lacking altogether.

Our aim was not to provide an exhaustive review for each disorder; only some notions on pathogenesis and mechanisms are provided. Nowadays, for each of the disease categories the reader can access other high-quality books and review articles, both in print and/or electronic versions. We, therefore, favoured a comprehensive description of clinical findings to permit diagnostic orientation, prognosis and management.

We also respected the style of the previous editions by providing, per chapter, a rather broad selection of references for further reading. At this point, allow us to thank the publishers for having agreed to respect the space-consuming alphabetical arrangement of the references. Being clinicians ourselves we know, when reading a chapter, how much more convenient it is to immediately identify who wrote a given reference and when. We also believe that having to hand a source of valuable references might prove to be at least as useful as searching in online. In that respect, and although all references were updated, we also asked the authors to include, whenever possible, seminal articles rather than ‘copying and pasting’ references to review publications.
Physicians caring for children with rare or common neurodevelopmental disorders must keep in mind that a ‘disease’ will always be defined as a disorder of structure or function typically manifested by distinguishing signs and symptoms, with aetiology probably being the most important factor influencing prognosis and outcome. Each diagnostic investigation, taken alone, no matter how sophisticated, provides only a hint towards diagnosis.

Child neurology is reaching a turning point. During its early adolescence the discipline focused on description of numerous disorders. Identifying and homogeneously classifying, as best as possible, these disorders led to a better understanding of underlying mechanisms and to the development of global care practices.

In the 21st century, the development of new technologies needs to be perceived not just as an easy road to diagnosis but as a tool for a better understanding of the causes and as a support for research in discovering novel treatments that will improve the clinical management of affected children.

We remain grateful to Jean Aicardi for his pioneering work. We would like to thank all our co-authors and the publishers for having accepted the challenge to maintain his teaching as reliably as possible, ensuring that it is available for future generations of child neurologists.

ALEXIS ARZIMANOGLOU
ANNE O’HARE
MICHAEL JOHNSTON
ROBERT OUVRIER
March 2018
Acknowledgements

ALEXIS ARZIMANOGLOU

I am grateful to the families of my patients who during all these years entrusted me with their most precious children and taught me how to listen. Allow me also to acknowledge my own family and personal friends for their constant support. A huge “thank you” to my students who later became my friends and colleagues practicing child neurology in so many different parts of the world. Particularly those with whom I had the pleasure to co-author some of the chapters of this book. Last but not least, I will always be grateful to all those colleagues from whom I learn and keep appreciating their advice: members of the Child Neurology Departments of the San Juan de Déu Hospital in Barcelona, the Robert Debré and Necker-Enfants Malades Hospitals in Paris, the HFME hospital in Lyon; the members of the Société Européenne de Neurologie Pédiatrique, the International League Against Epilepsy, the European Paediatric Neurology Society, the American Epilepsy Society, the U-Task force for paediatric epilepsy surgery, the steering committee of the European Reference Network EpiCARE; all co-authors of this book and my team full of excellence at the University Hospitals of Lyon. I am confident they will recognise themselves. Merci.

ANNE O’HARE

I am grateful to my co-authors Bruce Shapiro, Roberto Tuchman, Carey Matsuba, and colleagues who generously gave of their time to advise: Ailsa McLellan Paul Eunson, Kaseem Ajillogba, Lynne Bremner, Ruth Henderson, Dawn Lamerton and the families who generously granted permission for their imaging to be included.

MICHAEL JOHNSTON

I would like to acknowledge Andrea Poretti, MD a Pediatric neurologist and expert on the cerebellum who very unfortunately passed away before the book was published. Andrea was from Switzerland worked with us at Hopkins and Kennedy Krieger and mentored by Prof Thierry Huisman.

ROBERT OUVRIER

Apart from my co-authors, Manoj Menezes, Paddy Grattan-Smith, Elsdon Story, and Russell Dale, I gratefully acknowledge all those who gave advice, case histories or illustrations: Eugen Bolshhauser, Philip Britton, Chris Burke, Stephane Mathis, Shekeeb Mohammad, Michael Stevens, Chris Troedson, Jean-Michel Vallat, and Eppie Yiu.

Authors

CHAPTER 1
We acknowledge the help of the late Dr Andrea Poretti with this chapter.

CHAPTER 4
All new figures were provided in this chapter by Professor Laurent Guibaud, Department of Foetal and Paediatric Imaging, HFME, University Hospitals of Lyon, France.

CHAPTER 5
The valuable help of Dr Nicolas Deconinck Head of the Neurology Department, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles (ULB) in Brussels, Belgium and Dr Catheline Vilain the Department of Genetics, Hôpital Erasme, Université libre de Bruxelles in Brussels, Belgium are acknowledged.

CHAPTER 9
The invaluable assistance of Prof Jaume Campistol Plana, Head of the Child Neurology Department of Hospital San Juan de Déu (Barcelona, Spain) in reviewing this chapter and the foundational work done by Hélène Ogier on this topic in the previous editions of this book are acknowledged.
CHAPTER 10
We thank Professor Eugen Boltshauser, Professor emeritus
Department of Pediatric Neurology, University Children's
Hospital, Zürich, Switzerland; Dr Eppie Yiu Paediatric
Neurologist, NHMRC Early Career Fellow at the Department
of Neurology, Royal Children's Hospital Melbourne, Australia;
and Professor Elsdon Storey, Professor of Neuroscience,
Department of Medicine, Central Clinical School, Monash
University Melbourne Vic Australia 3004, for their invaluable
contribution to this chapter.

CHAPTER 12
Our late friend and colleague Dr Andrea Poretti, former
Director of Pediatric Neuroradiology research at Johns
Hopkins, and attending pediatric neurologist at Kennedy Krieger
Children's Hospital prepared several figures for this chapter.

CHAPTER 16
We acknowledge the medical and paramedical team at
the Paediatric Clinical Epileptology, Sleep Disorders and
Functional Neurology Department and of the Child Neuro-
logy Department at the University Hospitals of Lyon, France
and the valuable help of our PA Mrs Sophie Naous.

CHAPTER 26
We thank Dr Anna Sarkozy, Dr Adnan Manzur, Dr Pinki
Munot and Dr Stephanie Robb for the clinical activities in
the Dubowitz Neuromuscular Centre.

CHAPTER 27
I acknowledge the assistance of Dr Dan Connolly, Neuro-
Radiologist, Sheffield Children's Hospital who helped select
and describe the MRs used in the chapter. I am grateful to
the following colleagues at Sheffield Children's Hospital who
reviewed the respective sections: Dr Sally Connolly, Paediat-
ric Gastroenterologist/Hepatologist; Professor Paul Dmitri,
Paediatric Endocrinologist; Professor Heather Elphick, Respi-
ratory Paediatrician; Dr Jeanette Payne, Paediatric Haema-
tologist; Professor Ajay Vora, Paediatric Haematologist; and
Dr Jenny Welch, Paediatric Haematologist.
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Chapter 1

Fetal Neurology

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Fetal Neurology

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A BRIEF HISTORY OF FETAL NEUROLOGY

The earliest studies of fetal neurological function were focused on fetal motor activity, based on the observation of aborted human fetuses. In 1837, Erbkam published the first descriptions of ‘fetal’ movements from his direct observations of spontaneous miscarriages (Erbkam 1837). In the 1930s a Pittsburgh anatomist Davenport Hooker studied and filmed the activity of human fetuses from clinically indicated surgical abortions (Wilson 2014). The rapid development of fetal neurology in recent years has been driven by three major forces. The first major advance in fetal imaging, starting in the 1970s, provided the original real-time observation of the fetal morphology with 2D-ultrasound. The ability to view the fetus enabled the study of in utero fetal behaviour which in turn generated a school of mainly European investigators, led by the Austrian neuroscientist, Heinz Prechtl and his team (de Vries et al. 1982; Prechtl 1985). These investigators compiled a detailed developmental description of the emergence and evolution of fetal movements and began to apply their observations as a tool to assess the integrity of the developing nervous system. The second major stimulus for the nascent field of fetal neurology has been the advance in our understanding of neurology of the preterm newborn infant (‘ex utero fetus’) over the past 40 years. Finally, there has been a growing recognition that many of the major chronic diseases of childhood and adults have their origins in fetal life (Ravelli et al. 1998; Roseboom et al. 1999; Hales and Barker 2001) including neurological and psychiatric conditions such as attention deficit disorder, autism and schizophrenia (Geddes et al. 1999; Walker et al. 2015). In addition, the role of earlier fetal compromise in predisposing to catastrophic perinatal brain injury is now generally accepted and has focused studies onto the intrauterine support of fetal brain development.

Ongoing advances in the speed and resolution of fetal imaging continue to advance our understanding of the fetus and associated milieu. As the speed and structural resolution of fetal neuroimaging becomes increasingly sophisticated, so the diagnostic and prognostic expectations of the neurologist grow. Firstly, the increased structural resolution of particularly fetal MRI now detects smaller anatomic changes that require careful distinction from normal variation; this in turn demands an in-depth understanding of normal fetal brain development. Hereafter, an aetiological diagnosis is pursued, often with limited additional fetal neurodiagnostic tools. Particularly pressing issues include the neurodevelopmental prognosis and likelihood of recurrence in future pregnancies. Determining whether the neurological risks are likely to be progressive during and after gestation, as well as how the fetal brain will tolerate the hazards of labour and delivery, need to be considered. Based on the imaged phenotype additional diagnostic testing for genetic or environmental causes may be indicated. Gathering all available diagnostic information in a timely manner is particularly critical in situations where termination of pregnancy is an option. There may considerable pressure on the neurologist in situations where the outcome of the pregnancy may depend on their prognostic opinions. In addition, given the inevitable maternal stress triggered by an unknown fetal diagnosis, as well as the known adverse effects of maternal stress on the fetus, there is frequent pressure on the neurologist to formulate an opinion with limited data and without the benefit of a conventional physical examination of the fetus. If the pregnancy continues the neurologist should provide brain-oriented recommendations for the planning of labour, delivery and the transitional period, with the goal of minimising the risk of secondary brain injury.

The basic expertise needed by a fetal neurologist includes an in-depth understanding of structural and functional neuroembryology, the available neurodiagnostic tools and a first-hand experience of the long-term neurodevelopmental outcomes of the common fetal phenotypes. Although the field is still largely driven by dysmorphology it is inevitable that expertise around the environmental threats to the developing fetal brain will become essential with increasingly sophisticated fetal testing. This will require an understanding of the normal and pathological intrauterine milieu, basic principles of obstetrics, transitional physiology and pathophysiology, as well as the potential brain hazards confronting the fetus and newborn infant with congenital anomalies. In addition, counseling requires an understanding of the legal, cultural, religious and ethical considerations for each individual.

Currently, the practice of fetal neurology remains heavily influenced by standard obstetric protocols for fetal imaging, which vary across different regions. Specifically, most – but not all – fetal neurological concerns arise during the standard...
‘anatomy screening’ fetal ultrasound around mid-gestation. As such the majority of consultations are for suspected neurological anomalies on these screening studies and are therefore lesion driven. The future role of the neurologist in fetal care is likely to involve a more active role in the brain-oriented care of high-risk populations, such as the fetus with growth restriction, birth defects and complicated twin pregnancies.

The clinical discussions in this section will be confined to those most commonly seen in fetal neurology consultation and the territory covered is by no means exhaustive: many of the diagnoses more commonly made during postnatal period are discussed elsewhere in this book. The focus will be on conditions currently detectable in the fetal period rather than those diagnosed at birth or early infancy and are of presumed fetal origin.

### NEUROEMBRYOLOGY

#### NORMAL NEURAL TUBE DEVELOPMENT

Development of the human nervous system starts on day 15 post-conception (p/c) when a primitive streak of specialised neuroectoderm forms on the dorsal surface of the embryo. Hensen’s node is a small nodule at the rostral end of the neural plate which directs development of the anterior neural tube. **Dorsal induction** is responsible for the formation and closure of the neural tube as well as the three primary vesicles at the rostral end of the neural tube. **Ventral induction** leads to formation of the cerebral hemispheres, eye vesicles, olfactory bulbs, pituitary glands and part of the face while dorsal induction includes primary and secondary neurulation. **Primary neurulation** begins with formation of the neural plate and tube, ending when the neural tube is separated from the surface ectoderm by the intervening mesenchyme. Formation of the neural plate starts on day 17 p/c and is complete by day 18 p/c when the edges of the neural plate begin to elevate, folding over to form the neural tube (Fig. 1.1). The entire process of primary neurulation is under the inductive influence of the notochord and chordal mesoderm underlying the neural plate/tube. Closure of the neural tube starts on day 20 p/c at the level of the future rhombencephalon. The anterior neuropore at the rostral end of the neural tube closes by day 25 p/c and the posterior neuropore on day 28 p/c at the upper sacral level. In the process of neural tube closure several important events occur: understanding both the normal and disturbed evolution of these developmental events is essential for informed evaluation and counseling of these cases. First, the neural tube becomes separated from the cutaneous ectoderm (disjunction) which then closes over the midline. The neural tube then becomes encircled by the mesenchymal mesoderm which is interposed between the neural tube and dermal ectoderm. Exposure to the external surface of the neural tube induces the mesenchyme to differentiate into fatty tissue, a process thought to be responsible for the association between neural tube defects and lipomatous lesions. Finally with closure of the neural tube neural crest cells are formed that come to lie on the dorsolateral aspects of the neural tube, where they develop into the dorsal root ganglia, cranial sensory and autonomic ganglia, as well as other tissues. Disturbances in disjunction, either premature disjunction or failure of disjunction, underlie many of the congenital spinal lesions seen in clinical practice.

Closure of the posterior neuropore marks the start of **secondary neurulation** at the caudal eminence. Secondary neurulation occurs in weeks 5 and 6 p/c, forming the sacrococcygeal elements caudal to the closed posterior neuropore and proceeds without direct involvement of the neural plate and tube. As the embryo approaches 30 days p/c this caudal eminence undergoes canalisation with cyst formation and coalescence, ultimately forming the filum terminale and distal conus medullaris. Ventral induction, which extends from 4 to 20 weeks p/c, includes a number of major developmental events. From 4 to 6 weeks p/c, following closure of the anterior neuropore, a series of constrictions form three anterior neural tube vesicles (prosencephalon, mesencephalon and rhombencephalon) (Fig. 1.2). Hereafter, three major flexures, the mesencephalic, pontine and cervical flexures, form in the anterior neural tube.

---

**Figure 1.1 Development of the neural tube and neural crest.**

Fig. 1.1a shows the action of dorsalising signals from the ectoderm (e.g. bone morphogenetic proteins; BMP) and ventralising signals (e.g. sonic hedgehog, SHH) from the notochord on the developing neural plate. Fig. 1.1b shows folding of the edges of the neural plate to form the neural tube. Fig. 1.1c shows covering by the mesoderm and ectoderm over the closed neural tube, and separation of the neural crest tissues. The neural tube divided by the sulcus limitans into the dorsal alar and roof plates, and the ventral basal and floor plates. (Adapted from Ten Donkelaar, et al. Clinical Neuroembryology, 2nd edition, Springer 2014.)
Patterning of the neural primordium describes the process of regionalisation by which segmented cell differentiation occurs across the developing neuroaxis. Patterning is controlled by a precise spatial and temporal agenda of gene expression along the rostrocaudal, dorsoventral and mediolateral axes of the neural tube. Morphogenetic gradients of inductive signalling and gene expression along each of these axes determine the regional phenotype of neural cells. In this way the developing neuroaxis becomes divided along the rostrocaudal axis into segments or neuromeres, each with a floor, basal, alar and roof plate (Fig. 1.1). Specialised signalling centres called ‘secondary organisers’ develop at genetically determined sites along the neural tube to further refine the local neural identities along the rostrocaudal and dorsoventral axes. Three secondary organisers have been identified at the rostral edge of the neural plate (the anterior neural ridge), in the diencephalon (the zona limitans interthalamica) and at the midbrain-hindbrain junction (the isthmic organiser; IsO) (Vieira et al. 2010) (Fig. 1.3). These secondary organisers are responsible for the graded expression of dorsalising and ventralising factors that generate the ventral motor and dorsal sensory cells of the neural tube. Most important among the dorsalising factors are the bone morphogenic protein (BMP) family produced by the non-neural ectoderm of the roof plate (Fig. 1.1), while proteins expressed in the prechordal and floor plates by the sonic hedgehog (SHH) gene are the major ventralising factors.

**DISORDERS OF NEURAL TUBE DEVELOPMENT**

**DISORDERS OF PRIMARY AND SECONDARY NEURULATION**

**Dysraphism of the Entire Neural Tube**

*Craniorachischisis Totalis*, the most severe form of neural tube defect, results from complete failure of neurulation and leaves the neural plate entirely uncovered by mesodermal and cutaneous ectodermal structures. These lesions are obviously incompatible with life, the vast majority resulting in spontaneous abortion in early gestation.

**Dysraphism of the Anterior Neural Tube**

*Anencephaly* results from failed closure of the neural tube anterior to the point of first neural tube closure at the level of the lower brainstem-cervical junction (i.e. the foramen magnum). In the most severe forms it extends forward to the level of the anterior neuropore at the lamina terminalis, thereby leaving the entire dorsal surface of the cerebrum and brainstem uncovered. Neural structures are not identifiable above the brainstem by fetal imaging (Fig. 1.4) and the few children who survive pregnancy die soon after birth.

An alternative explanation for the pathogenesis of anencephaly is that it is not a disturbance in primary neurulation, but rather due to primary developmental failure of the overlying mesoderm (skull and meninges) and non-neural ectoderm.
Encephaloceles are localised defects of neural tube closure anterior to the foramen magnum with extracranial extension of a cystic structure containing meninges, neural tissue and cerebrospinal fluid (CSF) (Fig. 1.5). Venous structures are often included in the cyst or — if intracranial — anomalous venous drainage is common. If parts of the ventricular system are extracranial the term meningoencephalocystocele (Fig. 1.5c) is used: the large majority of encephaloceles are occipital (Fig. 1.5a) while less common sites are frontal (often extending into the nasal cavity; frontoethmoidal) (Fig. 1.5b), temporal and parietal encephaloceles. Anterior encephaloceles tend to have a more favourable prognosis. When the CSF-filled lesions contain no obvious brain parenchyma the term cranial meningocele is used (Fig. 1.5f). Occipital encephaloceles most commonly include occipital lobe tissue, as well as sometimes cerebellar and brainstem tissue. Low occipital encephaloceles (sometimes extending into the cervical spine) may be associated with downward herniation of the cerebellar tissue when it is known as the Chiari III malformation. Encephaloceles may be associated with other intracranial complications, including hydrocephalus (in up to half of patients), microcephaly, subependymal heterotopias and agenesis of the corpus callosum.

Encephaloceles are often skin-covered, in which case maternal and amniotic fluid alpha-fetoprotein (AFP) are normal. The pathogenesis of these lesions is likely to be multifactorial; they have been associated with environmental factors such as early gestational hyperthermia, irradiation, hypervitaminosis A and maternal diabetes. Encephaloceles may be associated with malformations in other systems as well as recognised syndromes such as Meckel-Gruber and Walker-Warburg syndromes.

**Figure 1.5** Anterior neural tube defects: (a) occipital encephalocele; (b) frontal encephalocele; (c) meningoencephalocystocele (with herniation of lateral ventricle); (d–e) frontoparietal calvarial encephalocele; (f) occipital meningocele (no neural elements).

DYSRAPHISM OF THE POSTERIOR (SPINAL) NEURAL TUBE

These lesions are located posterior to the point of initial neural tube closure, i.e. below the foramen magnum. Terminology describing the various spinal malformations has been used inconsistently, leading to confusion in the field and compromised counselling. Spinal dysraphism is a term used to describe a broad spectrum of anomalies that involve variable degrees non-fusion of the neural, vertebral and mesenchymal tissues of the spine. The term spina bifida refers to interruption of the bony vertebral closure around the spinal cord (Botto et al. 1999). Spinal dysraphic defects may be further categorised as open or closed depending on whether they are skin-covered or not. Examples of open spinal dysraphisms include myelomeningoceles and myeloschisis, while skin-covered, closed
dysraphic lesions include meningoceles and lipomeningoceles. These lesions are illustrated in Figure 1.6.

Open Spinal Dysraphism

Open spinal dysraphism (OSD) occurs from regional failure of neural tube closure in the third week of pregnancy. The fundamental defect in OSD is non-disjunction of the cutaneous and neural ectodermal tissues during closure of the neural tube, leaving the lateral edges of the neural tube in continuity with the skin. By obstructing the normal interposition of mesenchyme between the two ectodermal layers development of the vertebral column is impeded: failure of the cutaneous and neural ectoderm layers to separate prevents skin closure over the defect, leaving the ependymal-lined central canal of the open neural tube (the placode) exposed to the external surface. If the placode is flush with the skin surface the lesion is called a myelocyte (or myeloschisis). Conversely, when there is dorsal displacement of the neural tissue by an expanded anterior subarachnoid space that causes the placode to protrude beyond the skin lesion is called a myelomeningocele (Figs. 1.6a and b). The direct exposure of the spinal neural tissue and meninges to the amniotic fluid is thought to contribute to the neurological dysfunction in affected individuals, which has led to a ‘two-hit hypothesis’ in which the neurological outcome is thought to be determined not only by the underlying neural defect but also injury to the exposed neural tissue through chemical, inflammatory or physical insults (Adzick 2010).

The incidence of OSD lesions is around 0.5–1.0/1000 live births but occurs with considerable regional variability. The precise mechanism(s) for failure of neural tube closure remains unknown and in most cases the etiology is probably multifactorial, with the majority sporadic in nature (Shaer et al. 2007). Disturbances in folate metabolism have been invoked for several reasons, the first being that antenatal folate administration has decreased the frequency of OSD. Second, mutations of the methylene tetrahydrofolate reductase (MTHFR) gene – which result in disturbed folate metabolism – have been implicated in up to 20% of OSD (Christensen et al. 1999). In a small minority of individuals OSD occurs as part of syndromes such as aneuploides (especially trisomy 18), Meckel–Gruber syndrome (autosomal recessive) and Lehman syndrome (autosomal dominant) (Sepulveda et al. 2004; Hume et al. 1996). A number of teratogenic agents have been implicated including antiepileptic agents (valproic acid, carbamazepine) and vitamin A, as well as maternal factors such as diabetes, obesity and hyperthermia.

About 80% of myelomeningoceles develop between the thoracolumbar and lumbosacral levels (Fig. 1.7). The vast
The majority of myelomeningoceles are associated with hindbrain herniation or the Chiari II malformation, a lesion thought to result from leakage of CSF through the open spinal defect. Loss of CSF removes the necessary pressure support required to distend the rhombencephalic ‘ventricle’ (McLone and Knepper 1989) which plays an important role in posterior fossa development. The resulting small posterior fossa results in crowding of the neural structures, obliteration of the cisterna magna, downward displacement of the cerebellar tonsils and vermis and disturbed CSF dynamics. The hindbrain herniation may be progressive through gestation, while myelomeningoceles may be associated with other brain anomalies including callosal agenesis, tectal beaking, periventricular heterotopias, an enlarged thalamic massa intermedia and other migrational anomalies. Split cord malformations (including diastematomyelia), in which a bony or cartilaginous septum divides the spinal canal and any contents, may complicate up to 40% of myelomeningoceles (Schwartz and Barkovich 2012): these malformations may be difficult to identify prenatally.

Diagnosis of OSD can be made in several ways. In many developed countries screening tests of maternal serum AFP levels are available, with diagnostic tests including amniotic fluid levels of AFP and acetylcholinesterase, as well as fetal imaging. Maternal serum and amniotic fluid AFP are normal in closed neural tube defects. In the interpretation of AFP levels it is important to be aware of conditions that may affect the AFP values, including gestational age, fetal demise, twins and abdominal wall defects. Fetal US studies and particularly targeted fetal ultrasound and MRI studies are used to diagnose myelomeningocele, based on the spinal defect and associated signs such as the characteristic shape of the calvarium (the ‘lemon’ sign) and the crowded cerebellum (the ‘banana’ sign) by fetal ultrasound (Fig. 1.8). Microcephaly is common especially between 16–24 weeks but this often resolves spontaneously later in pregnancy, with macrocephaly developing in some individuals who develop hydrocephalus. Other associated features may include talipes equinovarus and hip dislocation. Karyo is indicated if other malformations are detected.

**Differential Diagnosis**

Differential diagnosis of OSD includes sacrococcygeal teratomas, as well as the skin covered closed neural tube defects, lipomyelomeningoceles, meningoceles and myelocystoceles.

The prognosis of OSD depends on a number of factors that may impact neurological function. Prognostic factors include the segmental level of the spinal lesion, the degree of posterior fossa crowding and hindbrain herniation, the development of hydrocephalus and the presence of associated cerebral malformations. More than 75% of infants with OSD survive into adulthood; however, despite intensive management 14% of infants with myelomeningoceles die before 5 years of age (Oakeshott and Hunt 2003). Neurological deficits may originate from the brainstem level in those with Chiari II malformations: in one large study of myelomeningocele survivors one-third of individuals developed feeding dysfunction, stridor or apnea events (McLone et al. 1985). Brainstem dysfunction in these infants may be delayed until after 3 months of age and increases the mortality rate to 35% (Oakeshott and Hunt 2003). Cognitive outcome in these infants depends on a number of factors including the presence of other cerebral anomalies, such as agenesis of the corpus callosum (ACC), cortical dysgenesis and periventricular heterotopias. These lesions may also underlie the approximately 20% of children with myelomeningoceles who develop seizures. Cognitive outcome in a large but earlier study showed an average IQ of 102 in children where myelomeningocele was not complicated by hydrocephalus, an IQ of 95 where a shunt remained uninfected and an IQ of 73 in children complicated by shunt infection. About 70% of myelomeningocele survivors have an IQ higher than 80 but only half are able to live independently as adults (Hunt 1990). With regard to motor function, movements may be seen by fetal ultrasound or in the early neonatal period at levels below the segmental level of the lesion but are...
then lost during subsequent days (Sival et al. 2004; Korenromp et al. 1986). Unaided ambulation can be expected for lesions below S1, while lesions above L2 are entirely or partly wheel-chair dependent. Children with lesions at L4/L5 levels will be ambulatory (with or without devices) about 50% of the time; when lesions are above the L2 level scoliosis can be expected to develop at some point. Urinary and fecal incontinence is almost universal in myelomeningocele: hydrocephalus – which develops in about 85% of individuals – (Dias and McLone 1993) may be caused by compression of fourth ventricular egress or from aqueductal stenosis which accompanies myelomeningocele in 40–75% of individuals (Gilbert et al. 1986). The vast majority of children with hydrocephalic OSD will require ventricular shunts, of whom almost half will develop complications in the first year after shunt placement (McLone 1983; Caldarelli et al. 1996).

Management of Open Spinal Dysraphism
Prevention should be the primary goal but is complicated by the multifactorial aetiology of open spinal dysraphism (OSD). Folate supplementation has resulted in a significant decline in the incidence of myelomeningocele; however, compliance with recommendations for folate supplementation remains disappointing. Folate supplementation is optimal and associated with an 83% reduction in OSD rate (Wald 2004) when taken at 4 mg/day for at least 3 months before conception. The optimal delivery mode after fetal diagnosis of an OSD lesion remains controversial: pre-labour Caesarean delivery was associated with improved lower extremity function at two years compared to vaginal delivery and Caesarean after onset of labour (Luthy et al. 1991). Among those with Caesarean after labour onset the outcome was better for those with intact amniotic membranes at delivery (Shurtleff et al. 1994). Other less rigorous studies have shown no difference in outcome between vaginal and abdominal deliveries (Merrill et al. 1998). The postnatal surgical management for myelomeningocele has not changed significantly in years and is essentially focused on providing skin closure, de-tethering the spinal cord and shunt placement where hydrocephalus is significant. Closure of an OSD usually occurs between 24–72 hours after delivery to decrease risks of infection; unless significant hydrocephalus is present at birth shunt placement may be deferred for several days to allow initial healing of the spinal lesion and assess the effects of decreased spinal leakage on CSF dynamics and ventricular size. Significant hydrocephalus may disrupt healing of the spinal repair and necessitate earlier shunt placement.

A three-centre randomised clinical trial (The MOMS Trial Adzick et al. 2011) comparing fetal versus neonatal myelomeningocele repair found that a fetal repair between 19 and 26 weeks’ gestation, for lesions between T1 and S1 spinal levels, was associated with a decreased incidence of shunt-dependent hydrocephalus by 12 months as well as a decrease in hindbrain herniation (Adzick et al. 2011). This procedure has become available at a number of centres in the United States and results from this expanded clinical deployment of the technique are awaited. Since these procedures involve closure of the spinal lesion with skin and dura through a hysterotomy approach it is unsurprising that significant concerns include scar dehiscence and preterm birth, emphasising the need for careful selection of candidates and adherence to protocol.

Closed Spinal Dysraphism (CSD)
These lesions, which include meningoceles, lipomeningoceles, lipomyelomeningoceles and myelocystoceles, are by definition skin-covered. Although they are often evident as mass lesions elevating the skin surface they are seldom associated with Chiari II malformations. Distinction in the fetal period between open and closed spinal dysraphism may be difficult in some individuals (Husler et al. 2009). Although meningoceles are rarely complicated by Chiari II lesions or hydrocephalus these can occur: conversely, myelomeningoceles and myelocystoceles may not develop Chiari II malformations, or these may occur late in gestation (Husler et al. 2009). The incidence of CSD is not decreased by antenatal folate supplementation. Meningoceles (Fig. 1.9) are CSF-filled meningeal sacs covered by skin usually containing no obvious neural elements. The underlying spinal cord is usually intact but may be malformed into a placode. In addition, other occult spinal lesions may be present and cord tethering may develop. Unlike the lumbar predilection of myelomeningoceles meningoceles are most common in the thoracic levels of the spine. When meningoceles occur in the lumbar region they are thought to arise from abnormal secondary neurulation (Tortori-Donati et al. 2001). The neurological outcome of meningoceles is usually normal.
or near normal, especially in early childhood, but later complications of cord tethering such as disturbances in continence and ambulation may develop. In the minority of meningoceles with placodes and neural elements in the sac, as well as Chiari II malformations, the outcome is significantly worse. A myelocystocele develops from hydromyelic distention of the central canal of the spinal cord that herniates through a defect in the overlying vertebral column but remains skin covered (Midrio et al. 2002). Myelocystoceles may occur in the lower cord (terminal myelocystoceles) or in the cervical region. Terminal myelocystoceles (Figs. 1.6 and 1.7) are of caudal mass origin and may be associated with other features of the caudal regression syndrome such as lower abdominal, pelvic, bowel or bladder malformations (Choi and McComb 2000). Severe bladder, bowel and lower extremity motor deficits are frequent complications of terminal myelocystoceles and Chiari II malformations may develop later in gestation. These lesions need to be distinguished from sacrococcygeal teratomas, omphalocele-exstrophy-imperforate anus-spinal defect (OEIS) complex and myelomeningoceles.

*Spinal lipoma.* Spinal dysraphic states are often associated with lipomatous tissue. The underlying basis for this association is likely to be premature disjunction (see above) of the neural and cutaneous ectodermal layers. If neural and cutaneous ectodermal disjunction occurs prior to complete neural tube closure the mesenchyme may become interposed between the leading edges of the closing neural tube, developing into lipomatous tissue thought to underlie the development of lipomyelomeningoceles and spinal lipomas.

*Lipomyelomeningoceles* are CSD lesions in which there is a skin-covered placode associated with a lipoma contiguous with the subcutaneous fat (Fig. 1.6); the lipoma covers the neural elements and prevents them from bulging through the overlying defect, while cord tethering is also common. These lesions are thought to result from premature disjunction of the cutaneous and neural ectoderm, with herniation into the central canal of the mesenchyme where it is induced to become fat, then interfering with primary neurulation: the brain is usually normal with no Chiari II lesion. These lesions have a far better prognosis than myelomeningoceles including continence (Atala et al. 1992), despite sometimes significant malformation of the lower cord (Sutton 1995).

*Caudal regression syndrome* involves a spectrum of malformations in the lower spine resulting from undergrowth or agenesis of the caudal cell mass. Although rare the risk of this condition is increased 200-fold in fetuses of mothers with diabetes: the outcome of this condition depends on the extent of the defect but often includes significant urological and orthopedic complications.

*Sacroccygeal teratomas* are a rare fetal-onset tumour, more common in females but more malignant in males, that may mimic spina bifida lesions. These teratomas may be cystic, solid or mixed and may protrude in several directions from the sacrum; however, there is no spinal dysraphism or Chiari II defect. These lesions may cause high-output cardiac failure in highly vascular cases which may result in polyhydramnios and fetal hydrops.

**NORMAL RHOMBENCEPHALIC DEVELOPMENT**

At around 5 weeks p/c formation of the mesencephalic and pontine flexures begins to define the future rhombencephalic domain (Fig. 1.2). The mesencephalic flexure at the intersection of the mesencephalon and rhombencephalon is the site of the future midbrain-hindbrain (MHB) junction and the pontine flexure causes widening of the neural tube and thinning of the dorsal hindbrain, the site of the future fourth ventricular roof. Subsequent development of the cerebellum and surroundings proceeds through several overlapping stages:

1. **Patterning of the midbrain-hindbrain junction** (Fig. 1.3) is a pivotal step in the subsequent development of the posterior fossa structures. A critical initial stage is the precise positioning of the isthmic organiser (IstO) at the MHB junction where it develops at the interface between expression domains of two mutually suppressing homeobox transcription factors i.e. Otx2 in the caudal midbrain and Gbx2 in the rostral hindbrain. Suppression by Gbx2 of Otx2 expression permits development of the cerebellum and suppression by Otx2 of Gbx2 expression permits development of the mesencephalic tectum. Disturbances in expression of these gene products result in disorders of rostrocaudal patterning and may cause abnormal gain, loss or transformation of the midbrain and hindbrain structures (see below) (Barkovich et al. 2009). Decreased Otx2 or increased Gbx2 expression will shift the midbrain-hindbrain junction rostrally and vice versa. Once positioned, the IstO becomes defined early by the key molecule it secretes, i.e. fibroblast growth factor (FGF) and FGF8 in particular (Crossley et al. 1996; Basson et al. 2008; Sgier et al. 2007). Development of the mesencephalic tectum is regulated by Fgf8a while cerebellar development is regulated by Fgf8b: these factors ensure regionally specific cell differentiation and migration occur to form the midbrain roof and the cerebellar roof plate. Maintenance of appropriate levels of FGF 8 are essential for medial cerebellar development including the vermis while lesions with marked vermis abnormalities are likely to be due to disruption of early IstO function. Mutations in FGF result in expansion of the roof plate at the expense of vermis progenitor expansion. The rhombencephalon is made up of eight rhombomeres, the first two (R1 and R2) being the origin of the future cerebellum; the vermis arises from the alar plate of R1 and the R1/R2 roof plates while the cerebellar hemispheres originate from the R2 alar plate.

Development of structures in and around the fourth ventricle roof is complex (Fig. 1.10) and developmental disturbances in
this region account for many of the posterior fossa lesions seen in clinical practice. Several lines of evidence suggest signalling from the overlying mesenchyme acting on the underlying neuroepithelium plays a critical role in normal posterior fossa development (Aldinger et al. 2009), while signalling from the overlying leptomeninges is critical for the normal development of the fourth ventricle roof. Although the forkhead box C1 gene is expressed only in the overlying mesenchyme and not in the cerebellar tissue itself, Fox c1 mutations are associated with cerebellar hypoplasia, mega cisterna magna and the Dandy-Walker syndrome. There is a well-known association between posterior fossa anomalies and neurocutaneous syndromes such as PHACES syndrome, comprised of posterior fossa anomalies, hemangiomata, arterial anomalies, cardiac/aortic anomalies, eye anomalies and sternal clefts (Mahadi et al. 2012).

Formation of the pontine flexure widens the neural tube, stretching and thinning the dorsal rhombencephalon into a diamond-shaped fourth ventricle roof (Fig. 1.10). At 10 weeks p/c a transverse crease, the plica chooroidea, forms across the fourth ventricle roof, dividing it into the anterior (AMA) and posterior membranous (PMA) areas. The plica chooroidea forms the future fourth ventricular choroid plexus, while the AMA contains neurons and normally becomes incorporated into the developing vermis, with the PMA containing ependymal tissue but no neurons: these features are important in understanding the prognosis of developmental anomalies in this region. Children with Dandy-Walker malformation (DWM) or vermian hypoplasia – which are of AMA origin – are more prone to neurodevelopmental impairment while those with isolated Blake’s pouch cyst or mega cisterna magna – which are of PMA origin – are usually developmentally normal.

A series of perforations develop in the fourth ventricular roof, beginning around the 9th–10th week p/c when the ependymal lining of the fourth ventricle roof herniates through the overlying dura just caudal to the plica chooroidea to form the Blake's pouch (Paladini and Volpe 2006). By the end of the 10th week p/c the Blake's pouch perforates to form the foramen of Magendi. Between 14 and 17 weeks p/c the lateral foramina of Luschka open, an event that may be delayed as late as 26th week and, in up to 20% of humans, may fail altogether.

**Development of the Cerebellar Hemispheres and Vermis** (Fig. 1.11a–d). Once the fundamental territory of the cerebellar anlagen is established development of the cerebellar hemispheres and vermis proceed through programmed events of neuronal proliferation, migration, differentiation and finally organisation into lobes and lobules. Cerebellar neuronal proliferation occurs in two major regions which arise from different dorsoventral domains of R1. The earliest proliferative activity occurs around 7–8 weeks gestation when the R1 alar plates expand along the rostral edges of the fourth ventricle roof. From this periventricular neuroproliferative zone inhibitory GABA-ergic cells migrate radially into the cerebellar anlage where they form the Purkinje cell layer and the deep cerebellar nuclei: these inhibitory cells, originating in the primary neuroepithelium, express Ptf1a and will become the primary efferent neurons of the cerebellum. At the end of the third month p/c neuronal proliferation accelerates in the secondary neuroproliferative zone along the dorsolateral banks of the fourth ventricle, the rhombic lips. Neurons generated here are excitatory glutamatergic neurons that express Atoh1. These rhombic lip precursor cells migrate tangentially in two major directions. Cells from the more dorsal rhombic lip regions migrate in a caudal direction to form the pre-cerebellar nuclei such as the pontine, inferior olivary and other nuclei. Other Atoh1 neurons migrate in the subpial plane to form the external granular layer, a highly proliferative transient germinal

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**Figure 1.10 Fourth ventricular roof development.** Diagram showing lateral and dorsal views of the posterior fossa roof. By 10 weeks gestation the fourth ventricular roof is divided into anterior membranous area and posterior membranous area by the developing choroid plexus.
zone. By 29 weeks p/c the external granular layer covers the entire external surface of the developing cerebellum causing granule cells to undergo a subsequent amplification phase within a transient superficial germinial layer, regulated by the Purkinje cells. Postmitotic neurons from the external granular layer migrate radially into the cerebellar body along Bergman glial fibres across the Purkinje cell layer to form the (internal) granular layer of the mature cerebellum. Through a combination of inward migration and apoptosis the external granule cell layer becomes de-populated in the months after birth.

As discussed below, vermian development is a major prognostic factor in patients with posterior fossa lesions: a detailed assessment is, therefore, important for informed counseling. Understanding of vermis development has changed in recent years. Contrary to earlier understanding it is now known that a single cerebellar anlage is responsible for the formation of both the cerebellar hemispheres and midline vermis, with the latter developing from the proliferation of the mesial primordium and not through fusion of the hemispheres. Vermis development is delayed initially relative to hemispheric development but then begins to accelerate during the third month of gestation. In the sagittal plane growth of the vermis starts at the midbrain-hindbrain junction, proceeds in a craniocaudal direction and is usually complete in this plane by 18 weeks (Bromley et al. 1994), although this may be as late as 24 weeks (Bronshtein et al. 1998) gestation when it completely covers the fourth ventricle, with the caudal edge reaching the level of the obex. At 18 weeks gestation the primary tissue separating the anterior and posterior lobes of the vermis is usually visible (Robinson et al. 2007). Much like the other major midline structure, the corpus callosum, most of the normal vermian growth in the craniocaudal occurs not at the caudal-most (inferior) leading edge but rather in the neovermis which lies just caudal to the primary fissure. Neovermian growth occurs late, meaning that when the craniocaudal extent of the vermis is less than expected this does not necessarily imply inferior vermian hypoplasia: careful evaluation of the vermis lobulation is required and it is advisable to use the overall term vermian hypoplasia until the precise region of growth failure has been identified. Once fully developed the vermis should have a normal gestational age-appropriate rostro-caudal length, for which there are charts (Imamoglu et al. 2013): the fastigium-declive line should divide the vermis such that there is 1:2 ratio between the anterior and posterior lobes. There is a relatively typical appearance of vermian lobules and fissures, which should all be visible by 27–28 weeks (Robinson et al. 2007).

The role of gene expression in the developing cerebellar primordium is discussed above, from initial patterning to stimulation of the primary neuroepithelial zones. In addition, normal development of the cerebellar hemispheres, vermis and fourth ventricular roof is dependent on signalling molecules.
Chapter 1 Fetal Neurology

Disorders of rhombencephalic development

Developmental anomalies of the cerebellum and brainstem may originate in any of the major stages of development. Disorders of patterning originate very early in development: the rhombencephalic malformations that result from such patterning disorders have been recognised relatively recently and are not as yet well described. The most fundamental hindbrain malformations show features of arrested development around 5 weeks p/c with incomplete flexing of the hindbrain, leaving a residual ‘kinked brainstem’ with often profound anomalies of cerebellar formation (Fig. 1.12) (Smith et al. 2005).

Disorders of fourth ventricle roof formation are often associated with abnormal posterior fossa fluid collections: disturbances in mesenchymal-neuroepithelial signalling are thought to play a common pathogenetic role in these conditions (Aldinger et al. 2009). These conditions are a common indication for neurology consultation and include the Dandy-Walker spectrum, mega cisterna magna, Blake’s pouch cyst and possibly cerebellar hypoplasia and arachnoid cysts (Barkovich et al. 2009).

Developmental disorders of cerebellar hemisphere and vermis include conditions that arise from inadequate proliferation of cells in the posterior fossa neuroepithelial zones and of their subsequent support: as noted above these disorders may result from primary disruption of proliferation in the ventricular zone, the rostral midline (vermis) and more lateral (hemispheric) rhombic lips, as well as migrational and organisational disturbances in the Purkinje cell layer.

There is lack of consensus about the diagnostic criteria and classification of posterior fossa malformations. Some view these malformations as a continuum ranging from severe DWM (with an enlarged posterior fossa) to mild DWM (with a normal posterior fossa), isolated vermian hypoplasia, Blakes pouch cyst (with a normal vermis) and mega cisterna magna (with normal neural structures) (Table 1.1).

Figure 1.13 provides distinguishing structural features of these lesions. The mesenchymal origin of bone and meningeal development is likely to underlie the association between abnormal FOXC1 function and the enlarged posterior fossa seen in both DWM and mega cisterna magna. It has been suggested that the expression of FOXC1 dysfunction may be related to the extent of the gene deletion, which in turn determines the severity of the posterior fossa anomaly (Aldinger et al. 2009).

FOXCl has also been shown to be critical for the normal differentiation and migration of the rhombic lip and roof plate derivatives (Aldinger et al. 2009). In addition, in FOXC1 deficient rodents there is significant expansion of the choroid plexus (Aldinger et al. 2009), possibly playing a role in the hydrocephalus that often complicates DWM. Consequently, it has been suggested that defects in genes expressed solely by the cerebellar primordium will result in vermian hypoplasia with or without hemispheric hypoplasia, whereas abnormal expression of genes in the overlying mesenchyme is associated with the entire spectrum from DWM vermian hypoplasia and MCM (Aldinger et al. 2009).

Prognosis for neurodevelopmental outcome in the fetus with rhombencephalic malformation is broad across both the spectrum overall, as well as within the specific diagnostic categories. Factors that influence outcome include extent and topography of the lesion, associated supratentorial malformations or complications (e.g. hydrocephalus) and the presence of dysmorphic, genetic or chromosomal syndromes. The integrity of cerebellar foliation has also been identified as an important prognostic factor (Boddaert et al. 2003). The nature of functional deficits for posterior fossa lesions of fetal onset differs in some respects from lesions acquired later in life: the classic motor signs, such as ataxia, intention tremor, nystagmus and dysmetria, are generally less prominent although hypotonia and motor delays are common. Conversely the cognitive, affective and behavioural consequences of early life cerebellar anomalies are now better appreciated and constitute a developmental form of the cerebellar cognitive-affective...
Part I  Fetal and Neonatal Neurology

syndrome (Brossard-Racine et al. 2015) seen in older individuals with cerebellar stroke or tumour (Schmahmann and Sherman 1997). The anatomic substrate for these ‘non-motor’ functions of the cerebellum has been elucidated by recent studies which demonstrate distinct ‘closed’ loop circuitry, not only with the primary motor cortex but with many other higher cortical centres such as the dorsolateral prefrontal cortex. The anatomical basis through which the cerebellum influences cortical activity is the ascending projections from the dentate nucleus (Strick et al. 2009).

DANDY-WALKER MALFORMATION

The diagnostic criteria for classic DWM are vermian hypoplasia, posterior fossa enlargement with elevation of the tentorium cerebelli and torcular Herophili, as well as cystic dilation of the fourth ventricle (Fig. 1.13). Although about 85% of infants develop hydrocephalus by one year of age (Barkovich et al. 1989) this may be delayed and is a complication rather than an essential diagnostic criterion for the DWM. DWM is a fundamental defect of rhombencephalic roof development, with formation of the large cystic component of this deficiency thought to result from failure of the normal uptake of the AMA into the developing vermis and possibly delay failure of foraminal development in the PMA. The redundant AMA then billows out, possibly driven by cerebrospinal fluid pulsations, leading to cyst formation and expansion of the posterior fossa. Neuropathological studies of the DWM have shown that all vermic lobules are present but hypoplastic, especially inferiorly, and that vermis development appears arrested at about the 12-week p/c level (Kapur et al. 2009; Russo and Fallet-Bianco 2007). It has been speculated that the superior to inferior gradient of increasing hypo/dysplasia of the vermis results from waning isthmic organiser influence with increasing distance (Robinson 2014). The anomalous structures in the DWM are of rhombic lip (rhombomere 1) origin, with largely normal development of the primary ventricular neuroepithelium derivatives, such as the Purkinje cells and deep cerebellar nuclei.

Prognosis of the DWM is highly variable and appears to depend upon the degree of vermian hypo/dysplasia and presence of associated cerebral and extracerebral anomalies. Specifically, if anomalous brain development is confined to the posterior fossa then the primary prognostic factor is lobulation of the vermis, with size of the cystic lesion and posterior fossa being irrelevant. Intellectual impairment, which occurs in about half of patients with DWM, is correlated with

<table>
<thead>
<tr>
<th>Entity</th>
<th>Posterior fossa size</th>
<th>Torcular angle</th>
<th>Vermis</th>
<th>Tegmentovermian angle</th>
<th>Fastigial recess</th>
<th>Cerebellar hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dandy-Walker malformation</td>
<td>Increased</td>
<td>Elevated</td>
<td>Hypoplastic</td>
<td>Markedly increased</td>
<td>Absent</td>
<td>Hypoplastic</td>
</tr>
<tr>
<td>Blakes pouch cyst</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Mega cisterna magna</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal/mildly increased</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Vermian hypoplasia</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypoplastic</td>
<td>Increased</td>
<td>Absent</td>
<td>Variable</td>
</tr>
<tr>
<td>Dandy-Walker variant</td>
<td>Normal</td>
<td>Normal</td>
<td>Hypoplastic</td>
<td>Normal or mass effect</td>
<td>Normal</td>
<td>Normal or mass effect</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or mass effect</td>
<td>Normal; elevated if in fourth ventricle</td>
<td>Normal</td>
<td>Normal or mass effect</td>
</tr>
</tbody>
</table>

Figure 1.13  Dandy-Walker malformation. (a) Sagittal fetal MRI in a 22-week gestational age fetus. (b) Sagittal and (c) axial MRI in early infancy. Note: Elevated torcular Herophili (*); enlarged posterior fossa (x); hypoplastic vermis (white arrow) and hemispheres (black arrows).
the disturbance in vermis lobulation (Boddaert et al. 2003). Management of the DWM is largely conservative unless significant hydrocephalus or compression effects of the posterior fossa cyst develop. Hydrocephalus is traditionally managed by CSF diversion techniques such as ventriculoperitoneal shunt. Other approaches including endoscopic third ventriculostomy with choroid plexus cauterisation (Warf et al. 2011), as well as cyst-peritoneal shunts and stents between the third ventricle and cyst, have been used (Mohanty 2003).

**Dandy-Walker Variant**

Elements of the DWM may be seen in other posterior fossa anomalies. This has led to the term Dandy-Walker variant, most often applied to patients experiencing vermian hypoplasia without the other criteria for classic DWM. This term has unfortunately become the default diagnosis for a broad spectrum of posterior fossa lesions with enlarged fluid spaces, leading to inconsistency in classification and prognostication. The existence of this entity is controversial and use of the term has been discouraged. Distinguishing the ‘Dandy-Walker variant’ not only from a DWM but also other conditions such as mega cisterna magna, vermian hypoplasia and Blake’s pouch cyst (see below) may be challenging but is important, since these latter conditions have a significantly better outcome. Typically the term Dandy-Walker variant has been used when there is agenesis/hypoplasia of vermis (distinguishing it from a Blake’s pouch cyst), with cystic enlargement of the fourth ventricle and rotation of vermis (distinguishing it from mega cisterna magna) but with a normally sited torcular and tentorium, i.e. a normal-sized posterior fossa. The Dandy-Walker variant is rarely complicated by hydrocephalus.

**VERMIAN HYPOPLASIA**

The vermis ‘covers’ the 4th ventricle in a rostro-caudal direction, a process usually complete by 18 weeks but may be as late as 24 weeks gestation. In one study (Patek et al. 2012) vermian hypoplasia diagnosed before 24 weeks gestation were ‘resolved’ by term 50% of individuals, whereas those diagnosed after 24 weeks gestation were all confirmed postnatally. Given the rostrocaudal growth of the vermis it has been assumed that the inferior vermian lobules are the last to form and that a decrease in the rostro-caudal diameter involves at least underdevelopment of the inferior vermis. This has given rise to the term inferior vermian hypoplasia when the longitudinal axis of the vermis is short and the anterior: posterior lobe ratio is less than 1:2 (Fig. 1.14). However, recent reports emphasise that the inferior lobules are actually the first to develop and failure of posterior lobe development and arrested downward growth of the vermis is likely to occur in most individuals as a result of growth failure of the later-forming neovermis, located just caudal to the primary fissure. Since it may be difficult, especially prior to late gestation, to distinguish the different lobules by fetal MRI it is probably wise to reserve diagnosis of inferior vermian hypoplasia to those patients where this can be demonstrated clearly.

Other syndromic forms of vermian hypoplasia include the *molar tooth malformations* seen in Joubert and related syndromes (Fig. 1.15). To date 27 gene mutations (Table 1.2) mostly autosomal recessive in inheritance, have been associated with Joubert syndrome: these differ in terms of associated systemic findings (including renal, hepatic, ocular, oral-facial-digital and hypothalamic hamartomas). The molar tooth sign consists of elongated thick and horizontally oriented superior cerebellar peduncles, a deep interpeduncular fossa, vermian hypo/dysplasia and variable cerebellar hemispheric findings.
In addition, 30% of patients have additional brainstem and supratentorial anomalies: in these disorders of axonal guidance the midline crossing defect involves the superior cerebellar peduncles and corticospinal tracts, however more than 90% have normal corpus callosum development.

Table 1.2  Joubert Syndrome and related molar tooth malformation disorders (JSRD)

**Joubert Syndrome:** A genetic disorder including neonatal respiratory hyperpnea and liver dysfunction associated with later development of eye movement abnormalities, ataxia and intellectual disability. MRI on axial views shows atrophy of the cerebellar vermis associated with the appearance of the roots of a molar tooth formed by the cerebellar peduncles. Children often develop mild retinopathy and nephropathy.

Most mutations are in genes that code for endothelial cilia so the disorder is called a ciliopathy.

Addition of additional related disorders has led to designation of JSRD [Joubert Syndrome and Related Disorders (Zaki et al. 2008) *Neurology* 70: 556–65].

In addition to Joubert Syndrome the following disorders with molar tooth sign are also included in JSRD:

- **COACH Syndrome:** Cerebellar vermis hypoplasia, Oligophrenia, Ataxia, ocular Coloboma, Hepatic fibrosis
- **CORS** (Cerebello-Oculo-Renal Syndrome) with congenital blindness and renal signs including renal failure
- **Oro-facial-digital syndrome type IV** with at least one oral facial sign (cleft lip or palate, tongue tumours, notched upper lip) and digital signs including polydactyly or bifid digits.

**Figure 1.15  Molar tooth sign.** MRI studies in the (a,b) fetal and (c,d) postnatal periods in a patient with Joubert syndrome showing thick horizontally aligned superior cerebellar peduncle (white arrows in a, c), molar tooth sign (white arrows in b, d) and deep interpeduncular cleft (black arrow in d).

In addition, 30% of patients have additional brainstem and supratentorial anomalies: in these disorders of axonal guidance the midline crossing defect involves the superior cerebellar peduncles and corticospinal tracts, however more than 90% have normal corpus callosum development.

**Blake’s Pouch Cyst**

Blake’s pouch (Blake 1900) is a normal dorsal evagination of the fourth ventricle ependymal lining through the midline foramen of Magendie. (Strand et al. 1993). This pouch normally perforates around 9 to 10 weeks p/c to allow communication.
between the fourth ventricle and subarachnoid space. Failure to perforate leads to formation of a cyst that enlarges the fourth ventricle, elevating the otherwise normal vermis and increasing the tegmento-vermian angle (Paladini et al. 2012) (Fig. 1.16). Diagnostic criteria for a Blake’s pouch cyst include fourth ventricular enlargement with mild-moderate rotation of a normally formed vermis (with widening of the tegmento-vermian angle) as well as a normally sized posterior fossa and cisterna magna. Although delayed or failed foraminal development may play a mechanistic role in both Blake’s pouch cyst and DWM there are a number of fundamental differences between these entities. These lesions originate from different regions of the dorsal hindbrain – the Blake’s pouch cyst being a developmental defect of the PMA – while the DWM is a developmental defect of the AMA. Although not easily seen with conventional imaging, identifying the fourth ventricle choroid plexus along the inferior surface of the vermis and roof of the cyst is a useful diagnostic sign of a Blake’s pouch cyst. Over half of Blake’s pouch cysts spontaneously resolve around 24–26 weeks gestation and almost two-thirds resolve by term, returning the vermis to a normal position, presumably due to delayed fenestration of the fourth ventricular roof (Paladini et al. 2012); such spontaneous resolution does not occur in DWM. Although hydrocephalus develops in a large majority of DWM hydrocephalus, even tetraventricular hydrocephalus, has been described in cases of Blake’s pouch cyst but this is an unusual finding. The torcular and tentorium are not elevated in Blake’s pouch cysts: although controversial, some authors consider Blake’s pouch cyst, Dandy-Walker variant and mega cisterna magna part of the same spectrum, with differences due to the degree and timing of Blake’s pouch fenestration (Robinson and Goldstein 2007). Diagnosis of a Blake’s pouch cyst is usually incidental, the clinical picture usually benign with a favourable long-term outcome.

MEGA CISTERNA MAGNA

The cisterna magna is the space between the inferior margin of the vermis and the posterior rim of the foramen magnum. The normal cisterna magna is between 3–8 mm and most consider 10mm or more to represent mega cisterna magna. Some authors propose the mega cisterna magna is a Blake’s pouch cyst remnant after partial or delayed foraminal opening have allowed the fourth ventricle to return to a normal size (Fig. 1.17) (Robinson and Goldstein 2007). Both mega cisterna magna and Blake’s pouch cyst may be associated with other anomalies but when isolated both have an excellent prognosis. In one study 90% of participants affected by isolated mega cisterna magna and Blake’s pouch cyst had normal neurological outcomes compared to only 50% of participants experiencing DWM or vermian hypoplasia (Gandolfi Colleoni et al. 2012).

ARACHNOID CYSTS

Posterior fossa arachnoid cysts (Fig. 1.18) are enclosed by the pia and arachnoid layers of the meninges and their contents have the same consistency as cerebrospinal fluid. Arachnoid cysts may enlarge to cause compression/distortion of the posterior fossa structures, including elevation of the vermis and/or obstruction of CSF drainage and hydrocephalus, although they do not communicate directly with the ventricular system.
Unless such complications occur posterior arachnoid cysts may remain remarkably asymptomatic.

CEREBELLAR HEMISPHERIC MALFORMATIONS

Anomalies of the cerebellar hemispheres may include hypoplasia, dysplasia or disruptions. Predominant hemispheric underdevelopment is uncommon but may be seen in the pontocerebellar hypoplasias (see below) and in survivors of extreme prematurity. Unilateral cerebellar hypoplasia is usually due to a developmental disruption often following cerebellar haemorrhage rather than primary dysgenesis. The two proliferative regions contribute unequal cell numbers to the future cerebellum, the rhombic lip-derived population far exceeding that from the primary ventricular neuroepithelium; however, the Purkinje cell layer (of ventricular zone origin) provides critical support for the massive proliferation of granule cell precursors (of rhombic lip origin) in the overlying external granular layer: this mitogenic support is mediated by the products of the sonic hedgehog (SHH) gene family (Hatten and Heintz 1995). Impaired neuronal proliferation in either of the two major germinal zones may therefore limit the normal massive expansion of the granule cell precursor pool, resulting in cerebellar hypoplasia. Since this expansion of the granule cell population continues through late gestation and into postnatal life cerebellar hypoplasia may manifest late in development (Malinger et al. 2009). Of note is that cerebellar hypoplasia due to SHH signalling defects affects vermis and hemispheric development equally while earlier isthmic organiser defects (see above) cause disproportionate vermis hypoplasia. Normal migration and organisation of the Purkinje cell layer is essential for normal granule cell proliferation while the Bergman glia (of ventricular zone origin) are responsible for normal...
Purkinje cell migration. Mutations in the reelin gene which disrupt cerebellar neuronal migration are a known cause of cerebellar hypoplasia. In summary, Purkinje cell migration defects are likely to underlie many forms of cerebellar hypoplasia.

Rhombencephalosynapsis is a cerebellar malformation with partial (20%) or complete (80%) ‘fusion’ of the cerebellar hemispheres and superior cerebellar peduncles, with midline continuity of the deep cerebellar nuclei (Fig. 1.19). The superior vermis is consistently absent although a wide range of associated brain anomalies may be present, including fused thalami and fornices, absence of the septi pellucidi, callosal agenesis and hydrocephalus, with features of aqueductal stenosis. On axial MRI views the fourth ventricle has a ‘diamond’ shape while the co-occurrence with holoprosencephaly suggests a disturbance in dorsal-ventral patterning; typically the transversely oriented cerebellar folia extend across the midline without interruption by the vermis. Most individuals have some degree of neurodevelopmental impairment but the range is very broad.

**PONTOCEREBELLAR HYPOPLASIAS**

Given the common origins of the cerebellum and certain brainstem regions it is unsurprising that developmental anomalies may co-occur in these structures. Cerebellar anomalies on fetal imaging warrant careful evaluation of the brainstem structures by fetal MRI: in general the presence of an associated brainstem anomaly implies a significantly worse prognosis for cerebellar lesions (Patek et al. 2012). One such group of conditions is the pontocerebellar hypoplasias (PCH) (Table 1.3), characterised by a small pons and varying degrees of cerebellar defect, even near-total absence (Barth 1993; Parisi and Dobyns 2003; Maricich et al. 2011). The neurodevelopmental prognosis is bleak, with global delay which is usually severe and progressive: unlike most other fetal rhombencephalic anomalies these autosomal recessive conditions have a primary developmental origin and subsequent progressive atrophy. Currently six forms have been described based on their clinical, imaging and pathology findings with some of these forms such as types 5 and 6 extremely rare. Type 1 PCH also has prominent anterior horn cell degeneration, resulting in bulbar dysfunction which manifests in the fetal period as polyhydramnios and later contributes to the respiratory and feeding complications that lead to early death, usually before the age of one. Type 2 PCH is associated with prominent microcephaly, dyskinesias and seizures; most affected children die in late infancy-early childhood.

**Pontine tegmental cap dysplasia** (Rauscher et al. 2009) (Fig. 1.20), another posterior fossa anomaly in which disturbed
axonal guidance has been implicated, consists of a flat ventral pons, a ‘cap’ or beak protruding from the dorsal pons into the fourth ventricle and severe hypoplasia of the middle and inferior cerebellar peduncles. It is associated with cranial neuropathies, most commonly of the eighth nerve. This condition is associated with hearing loss, facial anesthesia and paralysis as well as abnormal swallowing, while gross motor and cognitive deficits may also be present.

**NORMAL PROSENCEPHALIC DEVELOPMENT**

Between 3 and 5 weeks p/c three major vesicles form at the rostral end of the neural tube: the prosencephalon (the future telencephalon and diencephalon), the mesencephalon (midbrain) and rhombencephalon (metencephalon and myelencephalon) (Fig. 1.2). At this time the anterior neural tube develops three major flexures, the mesencephalic, pontine and cervical flexures. Ventral induction proceeds through a series of connected steps that include (1) formation, (2) cleavage and (3) midline development of the prosencephalon (Volpe et al. 2009).

**PROSENCEPHALIC FORMATION**

The prosencephalon divides into two secondary vesicles, the telencephalon and diencephalon, at around 5 weeks gestation. The telencephalon gives rise to the cerebral hemispheres, putamen and caudate nucleus while the diencephalon develops into the thalamus, hypothalamus, globus pallidus and optic vesicles.

**PROSENCEPHALIC CLEAVAGE**

During the early fetal period the forebrain is completely embedded in a solid meninx primitiva, which plays an important role in prosencephalic development. Around 35 days p/c the human telencephalon is cleaved into left and right vesicles, through a combination of increased apoptosis and decreased proliferation: these events are under the control of complex signalling pathways in the midline prosencephalon. Responsible signalling molecules include bone morphogenetic protein (BMP) and WNT (Fernandes and Hebert 2008; Hebert et al. 2002; Fernandes et al. 2007), expressed in the dorsal midline, fibroblast growth factor (FGF) in the rostral midline and SHH signalling in the ventral midline. During neural embryogenesis BMP and SHH have opposite, even antagonistic, patterning effects in the dorsoventral plane: disturbances in these relationships may result in the holoprosencephaly spectrum of anomalies (see below).

**MIDLINE PROSENCEPHALIC DEVELOPMENT**

The lamina terminalis forms the anterior tip of the neural tube. In the dorsal aspects of the lamina terminalis lies the commissural plate, which gives rise to three major commissures that link the two sides of the telencephalon. These commissures
develop under the attracting or repelling influence of molecules secreted by glial cells and, to a lesser extent, neurons in the prosencephalic midline (Fame et al. 2011; Nishikimi et al. 2013). The anterior commissure crosses in week 10, followed by the hippocampal commissure in week 11; a midline glial ‘sling’ develops at the future junction of the genu and body of the corpus callosum, with the first callosal fibres crossing in weeks 12 and 13, after which the callosum expands in both directions (Barkovich and Kjos 1988; Rakic and Yakovlev 1968; Achiron and Achiron 2001), while pioneer neurons originating from the cingulate cortex later cross the midline and enter the contralateral cortex (Koester and O’Leary 1994). Under the influence of specific guiding and growth substances present in the interhemispheric space, callosal fibres develop rapidly such that by weeks 14–15 all five parts of the mature corpus callosum (rostrum, genu, body, isthmus and splenium) are present, although short in rostral-caudal extent. The hippocampal commissure, which eventually lies below the isthmus-splenium junction, guides the crossing fibres of the future splenium, eventually the most prominent part of the callosum. Subsequent caudal-ward growth of the callosum is largely due to accelerated growth the anterior and central parts of the callosum, itself due to rapid expansion of the frontal cortices: consequently, the splenium is displaced backwards. The callosum reaches full longitudinal extent between by 19–20 weeks, after which it grows in thickness. Failure of the callosum to reach full longitudinal extent may be due to failure of any or all of these callosal elements to form. The fornix and adjacent septum extend between the anterior and hippocampal commissures as the callosum expands and pushes the anterior and hippocampal commissures further apart the fornix and septum pellucidum are stretched out into their final position.

Cavum Septi Pellucidi: The commissural plate also gives rise to the septal leaflets. The space between the septal leaflets forms one common cavity which is then divided into the cavum septi pellucidi anterior to the level of the foramen of Monro and the cavum vergae behind this plane (Raybaud 2010). The walls of the cavum septi pellucidi become apposed from back to front, starting at about 6 months gestation, closing completely in 85% of normal infants by 3 to 6 months postnatal. The cavum septi pellucidi is an important imaging landmark since its presence indicates that the corpus callosum must be present, at least partially, however, the converse does not apply and the cavum septi pellucidi may be absent even with an intact corpus callosum. The cavum velum interpositum (Fig. 1.21) may become enlarged and create diagnostic difficulties: it is bordered above by the columns of the fornices and hippocampal commissure and below by the tela choroidea of the third ventricle. The anterior extension of the cavum velum interpositum is at the foramen of Monro, while the internal cerebral veins course along the floor of the cistern and under the splenium of the corpus callosum to join the vein of Galen. The cavum velum interpositum extends posteriorly into the pineal region beneath the splenium of the corpus callosum, with the course of the internal cerebral veins displaced away from the splenium of the corpus callosum. The fornices are anatomic boundaries between the cavum vergae and the cavum velum interpositum, while the columns of the fornices are downwardly displaced with enlargement of both, resulting in a concave upper border of the cavum velum interpositum.

**DISORDERS OF PROSENCEPHALIC DEVELOPMENT**

The most fundamental disturbances of prosencephalic development include aprosencephaly (absence of telencephalic and diencephalic structures) and accompanying subset, atelencephaly (Fig. 1.22), in which the telecephalon is absent but diencephalon (including the thalami) persists (Marcorelles and Laquerriere 2010; Volpe et al. 2009; Li et al. 2011b): these lesions are rare and lethal.
Part I  Fetal and Neonatal Neurology

DISORDERS OF PROSENCEPHALIC CLEAVAGE

Holoprosencephaly (HPE) is the next level of disordered ventral induction and patterning. The resulting spectrum of anomalies results from complete or partial failure of prosencephalic cleavage. The fundamental mechanism is disturbed dorsoventral patterning, either under-ventralisation or over-dorsalisation. The SHH pathway is the major ventralising factor: disruption and resulting disturbed ventral induction is thought to be the common mechanism underlying development of the classic holoprosencephaly phenotypes. Since the dorsalising effects of BMP signalling have opposite, even antagonistic, effects on the ventralising actions of SHH, increased BMP signalling may also cause impaired ventral induction due to disrupted SHH signalling, leading to the holoprosencephaly spectrum of lesions (Fernandes and Hebert 2008). Since the dorsalising effects of BMP signalling have opposite, even antagonistic, effects on the ventralising actions of SHH, increased BMP signalling may also cause impaired ventral induction due to disrupted SHH signalling, leading to the holoprosencephaly spectrum of lesions (Fernandes and Hebert 2008). About 80% of infants with HPE have midface malformations but these have a very broad phenotypic spectrum, ranging from a single central upper incisor and mild hypotelorism to cyclopia with a proboscis. The incidence of HPE is around 1:10000 live-born infants but is much higher in aborted fetuses, affecting an estimated 1:250 gestations. These conditions have been classified previously into three grades of decreasing severity (alobar, semi-lobar, lobar) although this spectrum has recently been expanded to include syntelencephaly as well as ‘minimal’ (non-cleavage of the subcallosal/septal forebrain) and ‘microform’ HPE (not detectable by MRI) forms which have been proposed: recently a forme fruste of holoprosencephaly (‘interhypothalamic adhesion’) has also been proposed (Whitehead and Vezina 2014). Some authors consider septo-optic dysplasia to be part of the holoprosencephaly spectrum (Simon and Barkovich 2001; Li et al. 2011b), but here we consider it an anomaly of midline prosencephalic development (see below). The incidence of holoprosencephaly varies geographically and is significantly more common in spontaneous aborted fetuses.

Alobar holoprosencephaly (Fig. 1.23) is the most severe form in which prosencephalon is undivided with no midline cleavage. The forebrain is lined by predominantly entorhinal cortex with very little neocortex while typically there is fusion of the thalamic, hypothalamic and basal ganglia nuclei.
resulting in absence of the third ventricle. There is a large horse shoe-shaped monoventricle and a dorsal cyst while hydrocephalus is common, presumably due to the absent third ventricle. The olfactory bulbs, corpus callosum and cavum septi pellucidi, as well as interhemispheric fissure are absent, while optic nerves may be fused, absent or normal. Major facial and ocular defects are present more often than other forms, ranging from cyclopia to cebocephaly and ethmocephaly to the more common but less severe features of hypotelorism, cleft lip and absent premaxillary bony anlage. All forms of HPE may have a single or azygos anterior cerebral artery (ACA) but the alobar form may also have absence of the middle and anterior cerebral arteries. The presence of a single ACA may be useful in the fetal period for distinguishing mild forms of holoprosencephaly from septo-optic dysplasia (Bernard et al. 2002). The dorsal cyst is present in virtually all alobar forms and progressively less so in the semilobar and lobar forms, relating to the degree of thalamic fusion which causes the CSF to balloon out posteriorly. In \textbf{semilobar holoprosencephaly} (Fig. 1.24) the anterior aspects of the prosencephalon fail to separate as do the thalami, leaving transverse convolutions that cross the anterior midline and absence of the anterior corpus callosum, and a small or absent third ventricle. A monoventricle is present but with posterior aspects of the cerebral hemispheres appropriately cleaved with an interhemispheric fissure (IHF), usually an intact splenium, a posterior falk and no dorsal cyst. There is a spectrum of severity for semi-lobar holoprosencephaly and in the mildest form there may be cleavage of all but the most anterior aspects of the hemispheres: in fact, the precise distinction of the semilobar and lobar forms may be difficult. Both forms may be difficult to identify on the 18–20 ultrasound scan, and an absence of the cavum septi pellucidum may be the only clue (Winter et al. 2010): facial malformations may also be mild or absent.

\textbf{Lobar holoprosencephaly} (Fig. 1.25) has complete separation of the hemispheres except for the most ventral anterior regions, with a hypoplastic genu and absence of the cavum septum pellucidum (Winter et al. 2010). As such the interhemispheric fissure is present along the entire dorsal midline and the thalami are completely or mostly separated, with the third ventricle present and some frontal horn formation. The fused fornices appear as a linear structure running within the third ventricle from the anterior to hippocampal commissures: such intraventricular fused fornices may be a specific sign of lobar HPE (Pilu et al. 1994). The frontal horns of the lateral ventricles may be rudimentary but the third ventricle is usually fully formed, albeit often dysmorphic. The olfactory bulbs may be absent or hypoplastic, while facial anomalies may be minimal to absent.

\textbf{Holoprosencephaly} is most commonly associated with microcephaly although hydrocephalic macrocephaly may develop as a result of hydrocephalus due to aqueductal stenosis, which occurs in about 40% of individuals. Deep grey nuclear involvement is common in all forms of holoprosencephaly with some level of noncleavage essentially universal in the hypothalamus and very common in the caudate nuclei (96%), lentiform nuclei (85%) and thalami (67%) (Simon et al. 2000): in addition to these classic forms other variants of holoprosencephaly are now recognised. \textbf{Syntelencephaly} (Fig. 1.26) or the midline interhemispheric fusion variant, involves failed cleavage of the central frontoparietal regions of the cerebral hemispheres, with separation of the basal forebrain, anterior frontal and occipital lobes (Lewis et al. 2002). The genu and splenium of the corpus callosum are normally formed but the body is absent and there may be incomplete separation of the thalami and caudate nuclei. While the basal/ventral forebrain is most involved in the classic phenotypes the dorsal parts of the hemispheres are involved in syntelencephaly variant while the basal forebrain may be normal. Thus syntelencephaly is likely to represent not failure of ventralisation like other forms of HPE but rather disrupted dorsalisation due to either primary impairment of BMP expression or excessive SHH signalling with secondarily decreased BMP expression and disturbed dorsal induction (Fernandes and Hébert 2008). In syntelencephaly the sylvian fissures are often vertically oriented and continuous across the midline at the vertex (Simon and Barkovich 2001). Cortical dysplasias and subcortical heterotopias are present in over half of individuals.
experiencing syntelencephaly (Simon and Barkovich 2001) and within the same family a wide spectrum of holoprosencephalic phenotypic severity may be seen from most severe to essentially normal: endocrine anomalies may be associated with holoprosencephaly.

*Aetiology:* HPE appears to have a multifactorial aetiology with a complex inheritance pattern that includes both genetic and environmental factors. Holoprosencephaly is commonly associated with other extracerebral anomalies, including congenital heart disease (especially transposition of the great arteries), scalp defects, limb reduction defects and postaxial polydactyly. Abnormalities in chromosome number may occur in up to 45% of individuals including trisomies 13 (most common), triploidy (less common) and 18 (uncommon) (Olsen et al. 1997; Bellone et al. 2010). In addition, for up to 25% of individuals affected by holoprosencephaly this occurs in recognisable genetic syndromes such as Meckel-Gruber, Aicardi, Pallister-Hall, pseudo-trisomy 13, Smith-Lemli-Opitz and velocardiofacial syndromes. Genetic causes for HPE are found in about 20% of live-born cases (Bellone et al. 2010).

Some have proposed a multifactorial origin for HPE with interaction required between a genetic predisposition and environmental factors (Rosenfeld et al. 2010). Non-syndromic isolated HPE is usually inherited as an autosomal dominant condition associated with deletions or mutations in at least 12 specific gene loci including SHH, ZIC2, SIX3 and TGIF. The ZIC2 mutation has distinct facial features with upslanting palpebral fissures, bitemporal narrowing, large ears, short nose with antverted nares and a broad philtrum (Itoh et al. 2011), with clinical testing for these now available. Maternal diabetes increases the risk of HPE by up to 200-fold.

*Prognosis:* Although outcome is significantly worse among those with severe brain and facial dysmorphism even the more severe forms of holoprosencephaly are not uniformly lethal. About half of children with alobar HPE die by 5 months but up to one-third of infants survive beyond

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**Figure 1.25** Lobar holoprosencephaly in a 25-week gestation fetus. Fetal T2-weighted image showing fusion of the ventral forebrain, hypothalamus, and thalamus. (a) absence of the frontal horns of the lateral ventricles (top arrow) and small third ventricle (bottom arrow); (b) diencephalic fusion (solid arrow); (c) basal forebrain fusion (solid arrow).

**Figure 1.26** Postnatal MRI in an infant with syntelencephaly, the midline interhemispheric fusion variant of holoprosencephaly, with failed cleavage of (a) the central frontoparietal region and (b) thalami. The genu and splenium of the corpus callosum are normally formed (a, arrows), but the body is absent.
their first birthday (Barr and Cohen 1999). About half of children with lobar HPE will learn to walk, use their hands meaningfully and speak in single words or phrases. Survivors of HPE may develop a number of complications including neurodevelopmental and endocrine disorders such as diabetes insipidus, thyroid hypoplasia, adrenal hypoplasia, hypogonadism and growth hormone deficiency (Fernandes and Hebert 2008). Hydrocephalus is most common when a dorsal cyst is present.

DISORDERS OF MIDLINE PROSENCEPHALIC DEVELOPMENT

AGENESIS/DYSGENESIS OF THE CORPUS CALLOSUM

Current fetal ultrasound screening and MRI confirmation has changed our understanding of the incidence, associated findings and prognosis of ACC. ACC, partial or complete, is one of the most common referral diagnoses for fetal neurological consultation (Fig. 1.27). As discussed above, the corpus callosum forms from several different midline elements, with previous understanding of partial ACC being that the splenium was always deficient. Although partial ACC often appears fore-shortened in the anterior-posterior plane this is not necessarily due to failure of the posterior body, isthmus or splenium, to develop but may result from failure of any of the components of the corpus callosum to form or expand appropriately; consequently there are multiple variants of callosal hypo/agenesis.

Diagnosis: Fetal movements make fetal imaging of the corpus callosum challenging: reliable diagnosis of absence by fetal ultrasound may require considerable expertise. Fetal ultrasound has a false positive rate for ACC as high as 20% (Fratelli et al. 2007; Pilu et al. 1993; Vergani et al. 1994) and lacks sensitivity for detecting associated anomalies. Fetal MRI detects additional intracranial anomalies in more than 20% of patients (Sotiriadis and Makrydimas 2012) while postnatal MRI identifies further anomalies in another 15% of patients thought to be isolated ACC by fetal MRI (Santo et al. 2012). Neuroimaging findings supportive of the diagnosis of ACC include absence of the cavum septi pellucidi, a ‘high-riding’ third ventricle, colpocephaly, widening of the interhemispheric fissure and parallel orientation of the lateral ventricles. The frontal horns of the lateral ventricles may have a crescentic or ‘steer-horn’ configuration in the coronal plane, due to the bundles of Probst displacing the lateral ventricles (Fig. 1.27f) (Raybaud 2010).
Sulci on the medial cerebral surface of the hemispheres have a radial (‘sunburst’) orientation and Doppler ultrasound may show an abnormal vertical trajectory of the pericallosal arteries. Several types of midline cyst and lipoma may be present in the expected location of the corpus callosum (see below): these cysts are dorsal to the third ventricle with which they may or may not communicate.

ACC may be isolated or complex, i.e. associated with other malformations; distinguishing between these forms has important prognostic implications (Goodyear et al. 2001; Jeret et al. 1987). ACC has been associated with a large number of chromosomal disorders and more than 200 genetic syndromes (Huang et al. 2012). Most cases of ACC are complex but the reported incidence varies across studies, depending in part on the imaging modality and study design. Complex forms of ACC comprise between 50% to 90% of all cases (Santo et al. 2012; Tang et al. 2009; Hetts et al. 2006). Cerebral sulcal anomalies have been reported in half of all patients suffering from ACC cases and these include polymicrogyria, lissencephaly, pachygyria and schizencephaly (Hetts et al. 2006). Posterior fossa anomalies are also common, with DWM reported in up to one-third of individuals (Barkovich and Raybaud 2012). Other neurological syndromes that may include ACC are Aicardi (see below) and Walker-Warburg syndromes; myelomeningocele is also a common association.

Most individuals experiencing ACC display no syndromes. However, ACC has been described as part of at least 80 chromosomal, genetic and sporadic syndromes. Chromosomal anomalies, most commonly trisomies, are present in close to 20% of ACC overall (Santo et al. 2012; Li et al. 2012), although rarely in isolated ACC (Santo et al. 2012). Finally, certain inherited metabolic diseases may be associated with ACC including non-ketotic hyperglycinemia, as well as pyruvate dehydrogenase deficiency among others (Prasad et al. 2009).

**Prognosis:** With the advent of routine fetal ultrasound the detection of isolated ACC has increased. The reported prognosis of truly isolated ACC is highly variable (Goodyear et al. 2001; Moutard et al. 2003): in a recent report 75% of isolated ACC had favourable neurodevelopmental outcomes (Sotiriadis and Makrydimas 2012). To date no specific gene loci have been identified for isolated ACC: the presence of additional anomalies, such as sulcal anomalies and migration defects, are major determinants of outcome, a significant issue in countries where the threshold for legal termination is around 24 weeks gestation, since many of the critical processes in cortical development have not normally occurred by then. The rate of normal outcome in truly isolated ACC is variable but ranges from 40% to 75% in different studies (Li et al. 2012), severe abnormality in 10%, (Sotiriadis and Makrydimas 2012) with the mild-moderate neurodevelopmental abnormality in the remainder. Conversely, when ACC is associated with other cerebral or chromosomal anomalies virtually all children have major neurodevelopmental abnormalities (Noguchi et al. 2014).

**Aicardi Syndrome** (Fig. 1.28) is an X-linked dominant condition lethal in males which should be considered in the female fetus with ACC. The diagnosis can only be confirmed postnatally since other criteria must be met, including ocular anomalies (retinal lacunae or colobomata) which may not be detectable in the fetus and infantile spasms. In the female fetus Aicardi syndrome is more likely to occur when agenesis of the corpus callosum is associated with cortical dysplasia (especially polymicrogyria or heterotopias), posterior fossa lesions (cysts or cerebellar hypoplasia), subependymal cysts around the third ventricle or choroid plexus lesions (cysts or papillomas). Ventriculomegaly is usually present and often markedly asymmetrical, while vertebrocostal anomalies may be seen in half of patients displaying Aicardi syndromes. The neurodevelopmental prognosis is universally dismal.

**ACC with midline meningeal dysplasia.** In agenesis of the corpus callosum both midline cysts and/or lipomas may occur as manifestations of disordered mesenchymal development. The interhemispheric cysts can be broadly classed as communicating or non-communicating (Barkovich and Raybaud 2012): communicating or Type 1 midline cysts

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**Figure 1.28** Aicardi syndrome. Fetal MRI scan (a) at 26 weeks gestation showing agenesis of the corpus callosum, inferior vermian hypoplasia, abnormal and irregular sulcation pattern consistent with a trans-mantle dysplasia and possibly polymicrogyria. (b) Postnatal retinal image showing typical retinal lacunae.
are unilocular and usually not associated with other major cerebral or cortical dysgenesis. Although the falx cerebri is often hypoplastic or absent the primary mechanism of Type 1 cysts is upward expansion of the tela choroidea and third ventricle (‘high-riding’ third ventricle) rather than mesenchymal dysplasia. Type 1 single cysts can be further subclassified as Type 1A when macrocephaly and hydrocephalus are present: type 1B when 1A features are accompanied by developmental ventricular obstruction (thalamic adhesion, hamartoma); and Type 1C when microcephaly is present. Non-communicating or Type 2 midline cysts are multiloculated lesions, separate from the ventricles and resulting from cystic meningeal dysplasia. The cysts usually increase in size during gestation and children are usually born with hydrocephalus: these can be subclassified as Type 2A when accompanied by hydrocephalus and hydrocephalus are present: type 1B when 1A features are accompanied by development of the tela choroidea and third ventricle ('high-riding' third ventricle) rather than mesenchymal dysplasia. Type 1 single cysts can be further subclassified as Type 1A when macrocephaly and hydrocephalus are present: type 1B when 1A features are accompanied by developmental ventricular obstruction (thalamic adhesion, hamartoma); and Type 1C when microcephaly is present. Non-communicating or Type 2 midline cysts are multiloculated lesions, separate from the ventricles and resulting from cystic meningeal dysplasia. The cysts usually increase in size during gestation and children are usually born with hydrocephalus: these can be subclassified as Type 2A when accompanied by hydrocephalus alone, Type 2B (Aicardi syndrome; see above) and Type 2C when heterotopias and other anomalies of the head and brain are present. Interhemispheric lipomas associated with agenesis of the corpus callosum probably arise from abnormal differentiation of the meninx primitiva, which forms the leptomeninges.

Partial ACC (Fig. 1.29). The corpus callosum is not fully formed in anterior-posterior extent until 20 weeks gestation and the diagnosis of partial ACC prior to that time may be difficult. Although this lesion often appears to result from stunted growth of the posterior corpus callosum partial ACC may result from failed development of any one or more callosal elements. As discussed above the corpus callosum is formed from a number of separate elements which all arise rapidly between 13 and 14 weeks p/c: thereafter, growth in the anterior-posterior axis is the result of progressive addition of fibres to each of these elements and longitudinal growth.

Neocortical crossing fibres, especially from the frontal association cortex, are late additions to the callosum and their failure to grow will lead to a foreshortened corpus callosum: therefore partial ACC are not different degrees along a continuum but rather different malformations, each with a different developmental disorder, often with different genetic defects. In this condition the pericallosal arteries take an upward turn, at the posterior limit of the residual corpus callosum. Partial ACC is often associated with other genetic or chromosomal syndromes: reports of long-term outcome in these fetuses are highly variable.

**DEVELOPMENTAL ANOMALIES OF THE CAVUM SEPTI PELLUCIDI**

The cavum septi pellucidi is an important landmark in fetal neuroimaging. A well-visualised normal cavum septi pellucidi is reassuring for normal development of the central-midline forebrain and excludes many complex malformations. Conversely, absence of the cavum septi pellucidi is a potential marker for a range of other cerebral anomalies and failure to establish presence may be an indication for fetal MRI. Fetal ultrasound is usually capable of alerting to the absence of the cavum septi pellucidi; however, the paired columns of the fornix may mimic the cavum septi pellucidi on fetal ultrasound and be falsely reassuring (Pilu et al. 2005). Cerebral anomalies commonly associated with absence of the cavum septi pellucidi include the holoprosencephaly spectrum, septo-optic dysplasia, callosal dysgenesis/hypogenesis, severe hydrocephalus (especially in aqueductal stenosis) and schizencephaly (Fig. 1.30), usually in the frontoparietal regions. The septum pellucidum develops in conjunction with the anterior callosum, so when absence of the cavum septi pellucidi is associated with partial ACC incomplete posterior extension of the callosum results from failure of anterior callosal development. In such cases the hippocampal commissure may mimic the genu. Septo-optic dysplasia (De Morsier Syndrome) includes absence of the cavum septi pellucidi, hypo/dysplasia of the optic nerves/chiasm and hypothalamic-pituitary dysfunction. Prenatal diagnosis and counseling for septo-optic dysplasia is difficult because of the broad spectrum of associated presentations and it may be impossible to determine the severity of disease prenatally. For these reasons absence of the cavum septi pellucidi warrants careful early postnatal evaluation for the manifestations of hypothalamic-pituitary dysfunction such as hypoglycemia and electrolyte disturbances, as well as ophthalmological and endocrine evaluation. Septo-optic dysplasia is distinguished from milder forms of holoprosencephaly by a lack of fused thalami: it has been suggested this may be diagnosed by low levels of maternal estriol during pregnancy (Lepinard et al. 2005). Truly isolated absence of the cavum septi pellucidi, which occurs in a minority of individuals, is difficult to establish with certainty in the fetal period with current conventional MRI and postnatal imaging is warranted. The neurodevelopmental outcome of this
disorder is controversial and although some reports indicate good outcome (Damaj et al. 2010) others suggest severe psychomotor impairment may occur (Belhocine et al. 2005).

**DISORDERS OF THE FETAL CHOROID PLEXUS AND VENTRICLES**

**VENTRICULOMEGALY**

Cerebral ventriculomegaly is diagnosed in up to 1% of fetuses, making it a leading referral diagnosis for fetal neurological consultation (Melchiorre et al. 2009a; Gaglioti et al. 2009). Routine fetal anatomic ultrasound reliably identifies fetal ventriculomegaly and is an important tool for following ventricular size, configuration and evolution over gestation. However, it is an imaging sign that may require fetal MRI to establish the etiological diagnosis and provide reliable prognostication. The most reliable prognostic fetal neuroimaging features include the severity, progression, aetiology and presence of associated findings.

**Diagnosis and classification:** By convention fetal ventricular size is measured as the diameter of the lateral ventricular atrium on an axial view and is relatively stable at around 6–7mm during normal development between 14 weeks and term (Almog et al. 2003). A widely used criterion for diagnosing ventriculomegaly has been ventricular diameter ≥10mm (>4 standard deviations above the mean). A number of classification criteria have been used, albeit inconsistently (Melchioirre et al. 2009a; Sotiriadis and Makrydimas 2012; Guibaud 2009; Parilla et al. 2006; Glenn and Barkovich 2006), to categorise ventriculomegaly including mild, moderate, or severe, unilateral or bilateral, symmetrical or asymmetrical and transient, stable or progressive. Severe ventriculomegaly – which is uncommon – is applied when the maximal atrial width exceeds 15mm (Glenn and Barkovich 2006; Guibaud 2009; Gaglioti et al. 2009). Milder forms are far more common, which have been further categorised by some authors into mild (10–12mm) and moderate (12–15mm) forms. If the maximum ventricular diameter is <15mm then other anatomic anomalies are unlikely to occur. The most common scenario is milder degrees of ventriculomegaly, often unilateral or asymmetrical, which remain unchanged or normalise on follow-up studies. Conversely, when ventricular size is >15mm, the likelihood of spontaneous reversal is low; a small number of cases evolve to a severe form of progressive ventriculomegaly. Severe unilateral ventriculomegaly is rare and suggests either occlusion of the foramen of Monro or hemispheric tissue loss.

**Pathogenesis:** Several broad pathogenetic mechanisms may underlie ventriculomegaly. These include obstructed CSF drainage, underdevelopment of the cerebral parenchyma or injury and tissue loss around the ventricles. In this chapter the term hydrocephalus is used when obstructed CSF drainage is thought to be the underlying pathogenetic mechanism. The generic term ventriculomegaly will be used for ex vacuo forms of ventricular enlargement due to parenchymal hypoplasia or atrophy. Fetal imaging has advanced our understanding of ventricular development however commonly applied criteria for distinguishing between normal and abnormal ventricular size remain population-based statistical norms while outcome-based criteria remain lacking. Fetal head measurements may help distinguish between hydrocephalic and non-hydrocephalic ventriculomegaly, with large ventricles and large head circumference suggesting hydrocephalus; conversely, an accompanying small head is suggestive of an ex vacuo ventriculomegaly. Fetal hydrocephalus is present in the minority of fetal ventriculomegaly cases. Certain sites are more common for impeded CSF flow, including the aqueduct of Sylvius and the fourth ventricular foramina. Aqueductal stenosis is inferred when the lateral and third ventricles are enlarged and the fourth ventricle is normal in

![Figure 1.30](a) Fetal and (b) neonatal MRI scan showing absent cavum septi pellucidi with severe bilateral open-lip schizencephaly.
size. Aqueductal stenosis (Fig. 1.31) may result from brainstem dysgenesis, aqueductal forking, webs, membranes and nodules (e.g. hamartomas) (Fig. 1.31b, c) as well as from occlusion by hemorrhagic products and intrauterine infections including toxoplasmosis (Gay-Andrieu et al. 2003) and parvovirus B19 infection (Katz et al. 1996). Conversely, obstruction of fourth ventricular CSF egress through the foramina of Magendi and/or Luschka results in tetraventricular hydrocephalus. Such fourth ventricular obstruction may occur in several ways including posterior fossa crowding (in neural tube deficits and Chiari II malformations), posterior fossa cysts, masses, haemorrhage or DWM. Persistent Blake’s pouch with delayed opening of the foramina may sometimes underlie transient, self-resolving fetal hydrocephalus (Robinson and Goldstein 2007).

Aetiology: Congenital CNS infections are an etiological consideration in fetal ventriculomegaly but the positive detection rate based on maternal serology testing is highly variable. Postnatal studies in symptomatic children with known congenital cytomegalovirus (CMV) show a high incidence of mild-moderate ventriculomegaly (de Vries et al. 2004). However, ventriculomegaly is rarely the only feature and is usually associated with other features such as a periventricular ‘halo’, calcifications, pseudocysts, intraventricular synechiae as well as cortical and cerebellar malformations. In a review of previous studies (Devaseelan et al. 2010) evidence of congenital infections was present in 0.4% of mild ventriculomegaly (10–12mm) and 1.5% moderate ventriculomegaly (12–15mm) (Devaseelan et al. 2010). Conversely, others (Malinger et al. 2011) have reported a much higher incidence of positive maternal CMV serology in ventriculomegaly patients. Vauloup-Fellous et al. (2014) reported that an IgG avidity assay can distinguish between a recent primary infection and past infection, which may be useful for tailoring antibiotic treatment to prevent deafness in actively infected individuals. Toxoplasmosis is a rare case of ventriculomegaly and usually results from aqueductal stenosis. The usual complication of fetal parvovirus B19 infection is fetal anemia, but mild ventriculomegaly may also be seen (Weiland et al. 1987; Hartwig et al. 1989). Dysmorphic ventriculomegaly is most commonly seen in individuals affected by callosal dysgenesis when the ventricles retain a fetal configuration called colpocephaly in which the frontal horns are relatively normal while the posterior aspects are significantly enlarged with a tear-drop shape (Pilu 1993); in one large study of 430 individuals affected by ventriculomegaly 13% had ACC (Li et al. 2012). Chromosomal disorders, especially aneuploidy, may be associated with fetal ventriculomegaly however when ventricles are ≤15mm the detection rate for chromosomal anomalies is low, around 5% or less (Li et al. 2012; Gaglioti et al. 2009). Conversely, ventriculomegaly of any size associated with other fetal anomalies has an aneuploidy rate >15% (Bromley et al. 1991; Pilu et al. 1999; Mercier et al. 2001; Gaglioti et al. 2005).

Differential diagnosis: Ventriculomegaly is usually readily recognised by experienced ultrasonographers but may on occasion be mistaken for other fluid-filled supratentorial lesions such as hydranencephaly (Fig. 1.32), holoprosencephaly (Figs. 1.23–1.25) or enlarged cavum septi pellucidi or cavum velum interpositum (Fig. 1.21).

Prognosis: Factors known to have prognostic importance in fetal ventriculomegaly are the underlying mechanism (hydrocephalic, dysgenetic, hypoplastic/atrophic), rate of
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progression, the aetiology, associated parenchymal brain anomalies, associated syndromic-dysmorphic features or chromosomal anomalies and the ventricular configuration. An important reason for fetal MRI brain studies in fetal ventriculomegaly is to identify associated brain anomalies: with such methods the additional diagnostic yield for associated brain anomalies ranges from 5% to 60% (Salomon et al. 2006; Morris et al. 2007; Hannon et al. 2012) and these significantly increase the risk of adverse neonatal and long-term outcome (Nicolaides et al. 1990; Gaglioti et al. 2005). The likelihood of finding associated brain malformations increases with increasing ventricular size, reaching as high as 60% when ventricles >15mm (den Hollander et al. 1998; Gaglioti et al. 2005; Breeze et al. 2005; Hannon et al. 2012; Falip et al. 2007; Weichert et al. 2010). Most but not all studies (Gaglioti et al. 2005, Pilu et al. 1999, Goldstein et al. 1990) report a low rate of associated anomalies when ventricles are <15mm. Serial ultrasound is usually adequate to monitor the course of ventricular enlargement. Mild isolated unilateral, non-progressive ventriculomegaly usually remains stable or spontaneously resolves itself, has no significant associated findings and has a favourable neurodevelopmental outcome (Pagani et al. 2014; Pasquini et al. 2014; Melchiorre et al. 2009b; Melchiorre et al. 2009a). Spontaneous resolution occurs in almost half of patients ≤12mmHg and in 25% of those between 13 and 15mm (Melchiorre et al. 2009b, Melchiorre et al. 2009a; Parilla et al. 2006) while 16% show significant progression of ventriculomegaly (Parilla et al. 2006). In isolated and mild ventriculomegaly (<15mm) the actual ventricular size has no prognostic significance (Melchiorre et al. 2009b) while ventriculomegaly of >15mm rarely resolves spontaneously. In one study children with fetal diagnosis of mild isolated ventriculomegaly who had persistent ventricular enlargement at 2 years of age were at risk for mild fine motor and expressive language delay (Lyall et al. 2012). In patients experiencing isolated ventriculomegaly on fetal MRI the additional yield for associated anomalies detected by postnatal MRI ranges from 10 to 28% (Goldstein et al. 1990; Patel et al. 1994; Pilu et al. 1999; Mercier et al. 2001; Breeze et al. 2005; Hannon et al. 2012).

DISORDERS OF THE CHOROID PLEXUS

The choroid plexuses develop between 6–7 weeks p/c, starting in the fourth ventricle, but becoming most voluminous in the lateral ventricle and by 20 weeks having an adult configuration. The choroid plexus starts as neuroepithelial projections that go on to form the choroidal villi: within the matrix small tubules or cysts form from pinched off sections of neuroepithelium.

Choroid plexus cysts (Fig. 1.33) can grow but usually stay <10mm in size and are most commonly seen in the 2nd trimester when they are detected in up to 1% of fetuses. These cysts are rarely diagnosed before 16 weeks p/c and most resolve by 24 weeks p/c. Choroid plexus cysts have been associated with chromosomal disorders, and are seen in up to 50% of trisomy 18 patients but are rare in trisomy 21 (Bromley et al. 1996). Bilateral choroid plexus cysts and subependymal germinolysis have been associated with congenital viral infections including CMV (Herini et al. 2003); however, isolated choroid plexus cysts diagnosed prenatally are not associated with developmental disorders (DiPietro et al. 2011) Choroid plexus papillomas are rare tumours in the fetus, usually presenting with hydrocephalus due to excessive CSF production and potentially from foraminal obstruction (Verma et al. 2014).
NORMAL CEREBRAL CORTICAL DEVELOPMENT

NEURONAL PROLIFERATION

The central ‘ventricle’ of the neural tube is preserved in some configuration along the entire developing nervous system. The lining of this ventricular system contains the primary neuroproliferative regions responsible for cellular population of the brain and spinal cord, as well as distinct regions responsible for specific neuronal populations of the future cerebrum. In addition it is now known that cells migrating away from these primary neuroproliferative zones are capable of setting up important secondary germinal zones where cellular proliferation continues or resumes: examples of such secondary sites include the subventricular zone and external granular layer of the cerebellum (discussed below). The future forebrain or prosencephalon is divided on each side into a basal and alar plate (Fig. 1.1), each of which contains neuroepithelial sites for cellular proliferation that produce neurons with distinctly different destinations, migratory pathways and functions. The alar plate (or pallium) of the dorsal telencephalon is lined by a smooth sheet of neuroepithelium, the ventricular zone, which generates the excitatory glutamatergic pyramidal neurons of the cortex. The neuroepithelium of the ventral telencephalon (the subpallium) expands into two major proliferating cell masses, the lateral and medial ganglionic eminences (LGE and MGE), structures that form the diencephalon and basal ganglia and generate the inhibitory GABA-ergic interneuronal population of the future cerebral structures. The lateral ganglionic eminence is of telencephalic origin and will form the caudate and putamen, while the medial ganglionic eminence is of diencephalic origin and will form the globus pallidus. Certain neuronal populations, including the GABA-ergic interneurons, may continue to proliferate after birth in humans (Sanai et al. 2011; Malik et al. 2013). Early proliferation in the ventricular zone is asymmetrical, i.e. one daughter cell remains a progenitor while the other daughter cell becomes a postmitotic neuron or glial cell. Early intermediate progenitors resulting from asymmetrical proliferation of radial glial lineages move away from the ventricular surface to the subventricular zone (SVZ) where they become a major source of later migrating cells, mainly neurons. Radial glial cells also generate astrocytes and oligodendrocytes, with projection neurons of the deeper cortical layers being primarily generated by the ventricular zone while the subventricular produces neurons of the more superficial cortical layers.

In summary, the early excitatory neocortical projection neurons arise primarily from the dorsal (pallial) ventricular zone and later form an intermediate population of progenitors in the pallial subventricular zone. Conversely, interneurons arise from both progenitors in the ventral (subpallial) ganglionic eminences as well as the ventricular/SVZ (Letinic et al. 2002). The superficial cortical layers arise mainly from later-born progenitors from the SVZ, a type of transit amplifying progenitor generated from radial glial progenitors (Tarabykin et al. 2001).

The SVZ is a secondary neuroproliferative region that comes to lie between the ventricular zone and the intermediate zone. It is formed by cells generated in the underlying ventricular zone and in turn generates later migrating cells, mainly neurons but also glial cells. Whereas the ventricular zone generates the projection neurons of the deeper neocortex later neurons of SVZ origin populate the more superficial layers. In late gestation and the early postnatal period the SVZ expands greatly while the ventricular zone shrinks to an ependymal layer of one cell in thickness lining the ventricle. After their neuronal guiding function is complete the glia produce neurons, astrocytes and oligodendrocytes: the cellular progeny of radial glial cells in the subventricular zone remain an ongoing source of stem cells in the mature brain capable of generating neurons.

NEURONAL MIGRATION

Neuronal migration is a complex series of events under the guidance of numerous substances (mainly glycoproteins) in the extracellular space interacting with surface and other markers on the migrating cell (Fig. 1.34). Together these interactions generate distinct molecular signals that trigger the onset, continuation and cessation of migration: disturbances in this highly coordinated process result in the neuronal migration defects discussed below. The migrating cells move along the surfaces of other structures such as glial cells (gliophilic migration), the principal guides for radial migration and neuronal axons (neurophilic migration) primarily involved in interneuronal tangential migration. More recently a vasophilic form of migration has been described, in which blood vessels are used as guides. Broadly speaking there are two forms of migration: radial and tangential.

There are two forms of radial migration. In the very earliest stages, when the cerebral wall is very thin and the cell is able to connect with both the ventricular and pial surfaces, the nucleus migrates out to the surface (somal translocation), followed by retraction of the ventricular edge of the cell. These earliest migrating cells will form the pre-plate which is eventually split into the marginal zone (which includes Cajal-Rezius cells) and the deeper subplate zone. Radial glial cells become the primary mode of radial migration as the cerebral mantle thickens. Clonally related neurons migrate out toward the periphery along these radial glial fibres. Radial glial cells leave the VZ clustered in fascicles, but upon reaching the subplate they defasciculate and enter the cortex as individual fibres. Of note is that this interface between the intermediate and subplate zones is an important site for the development of heterotopias (see below).
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which includes axonal development and connectivity, neurite outgrowth, synaptogenesis, programmed cell death (apoptosis), glial proliferation and differentiation. These processes are responsible for the major third trimester increase in brain growth with 50% of cortical volumetric growth occurring in the final 6 weeks of gestation.

The subplate zone is a transient layer of neurons that plays a critical role in cortical organisation, synaptic development

Figure 1.34  Diagram showing radial (white dashed arrows) and tangential (blue dashed arrows) neuronal migration. 1, excitatory projection neuron migrating along radial glial cell; 2, inhibitory interneuron undergoing tangential migration; MGE, medial ganglionic eminence; LGE, lateral ganglionic eminence; SV, subventricular zone, IZ, intermediate zone; MZ, marginal zone.

Tangential migration is the principal mode of migration for inhibitory interneurons generated in the ventral neuroepithelium of the ganglionic eminences. In the ventral telencephalon proliferation of GABA-ergic interneurons becomes evident as early as 6–7 weeks p/c, resulting in two thickened regions of the periventricular zone, the medial and lateral ganglionic eminences. After leaving the neuroepithelium these interneurons initially migrate along a circuitous tangential path parallel to the cortex, doing so in three streams, moving through the subventricular, intermediate and marginal zones: once in the dorsal telencephalon these neurons switch their migration radially to their destination in the cortical plate. The ganglionic eminences generate the vast majority of cortical interneurons however an additional subpopulation of interneurons is generated in the SVZ of the dorsal telencephalon. More recent studies have shown that many GABA-interneurons arise from the ventricular/SVZ and migrate radially into the cortex (Letinic et al. 2002).

CORTICAL ORGANISATION

An important characteristic of the developing nervous system is the critical role played during specific periods by transient structures, such as the ganglionic eminences and periventricular germinal matrices, the subventricular zone, and the external granular layer of the cerebellum (see below).

By 20–24 weeks gestation migration is largely complete, leaving a cerebral mantle with a characteristic lamination pattern (Fig. 1.35) consisting of the ventricular zone, subventricular zone, intermediate zone, subplate zone, cortical plate and marginal layer. Hereafter, the major events in brain development are focused on cortical organisation (or re-organisation)

Figure 1.35  (a) Cerebral lamination in 20-week gestational age fetus by fetal MRI and by (b) histology showing the ventricular (VZ) and intermediate (IZ) zones, as well as the subplate (SP), cortical plate (CP) and ganglionic eminence (G). Part (a) reproduced from Pugash et al. Sonographic assessment of normal and abnormal patterns of fetal cerebral lamination. Ultrasound Obstet Gynecol 40: 642–52 © 2012. with permission from John Wiley and Sons Ltd. Part (b) reproduced from Rados et al. In vitro MRI of brain development. European J Radiol 57: 318–98. © 2006, with permission from Elsevier and (b) Rados et al. European J Radiol, 2006; 57: 187–98.

which includes axonal development and connectivity, neurite outgrowth, synaptogenesis, programmed cell death (apoptosis), glial proliferation and differentiation. These processes are responsible for the major third trimester increase in brain growth with 50% of cortical volumetric growth occurring in the final 6 weeks of gestation.

The subplate zone is a transient layer of neurons that plays a critical role in cortical organisation, synaptic development
and connectivity. Subplate neurons are among the earliest to migrate out from the ventricular zone to form the original preplate. Subsequently, cortical plate neurons are generated and these migrate out to split the preplate into two layers, the outer molecular layer and inner subplate. Next, the subplate undergoes rapid differentiation and transiently expresses a variety of receptors for neurotransmitters and growth factors, making it the site of the earliest synaptic activity, functional activity and connectivity. This rapid growth of the subplate zone peaks between 22 and 34 weeks gestational age. The subplate is the critical functional link between waiting afferents and their cortical targets. Specifically, this is the site of initial synaptic contact and ‘pioneering’ guidance between ‘waiting’ thalamocortical afferent axonal projections and cortico-subcortical efferents. Thalamocortical and trans-callosal axons, two major afferent systems forming the core of the gyral white matter, share ‘waiting’ periods in the subplate prior to their growth into the cortical plate. The subplate has an abundant hydrophilic extracellular matrix rich in signalling molecules critical for axonal guidance, normal cortical connectivity and structural plasticity. The subplate neurons elaborate a dendritic tree to receive synaptic input and send axonal projections to the cortex and to the subcortical nuclei: at this stage the subplate is the most active layer of the developing cortex in generating action potentials and has the synaptic apparatus for most cortical neurotransmitter systems including monoaminergic and cholinergic arousal and activating systems.

Around 24–25 weeks gestation the majority of thalamocortical axons are residing transiently in the superficial subplate while some have begun to enter the cortical plate to take up their permanent positions, establishing the necessary anatomic substrate for extrinsic cortical input from both the sensory and associative nuclei of the thalamus. The developing cortex is now poised to transition from spontaneous endogenous activity to a sensory-expectant form of functioning. Between 26–28 weeks gestation thalamocortical afferents continue to arrive in layers III and IV of the cortical plate, establishing the first synapses in a deep to superficial pattern. By 31–33 weeks gestational age connectivity between the thalamocortical axons and cortical layer IV becomes established setting the stage for functional sensory-driven development. Functional thalamocortical synapses are necessary but not sufficient for conscious cortical processing. Between 31–34 weeks gestational age primary gyri and sulci begin to appear and the cortex develops a six-layered pattern: hereafter the subplate plays a critical role in the accelerated development of cortico-subcortical and transcallosal cortico-cortical development. Neuronal network connectivity follows a broadly consistent pattern during development, with long-range connections developing well in advance of shorter cortico-cortical connections. Early synaptic activity in the developing cortex regulates axonal and dendritic growth and branching leading to thalamo-cortical, cortico-cortical and cortico-thalamic connectivity (Mire et al. 2012). Between 35 and 37 weeks gestational age interhemispheric synchronisation becomes established and by 38 weeks gestational age there is maturation of long intra-hemispheric (associative) and interhemispheric (callosal) cortico-cortical connectivity. Between 35 and 37 weeks gestational age there is intense development of inter- and intra-hemispheric connections, accompanied by major changes in the electrocortical activity.

Regression of the transient subplate layer begins around 27 weeks gestation with developmental apoptosis of subplate neurons and continues into postnatal life until about 90% of subplate neurons have been pruned. During this subplate regression the abundant hydrophilic extracellular matrix shrinks, making it less distinct on fetal MRI. Residual subplate persists longest in the gyral crests than in the depths of sulci, particularly in the associative cortical regions, presumably because of the ongoing role of the subplate in the prolonged development of long cortico-cortical associative circuitry and postnatal shaping of tertiary gyri. In the prefrontal associative cortex the remnants of subplate persist over the first 6 postnatal months.

**Synapse formation.** The normal processes of synapse formation and pruning have major temporal differences across the different regions of the brain. In each region there is an initial accumulation of synaptic density to a peak, followed by active apoptotic pruning. The earliest regions to embark on this course are the brainstem and cerebellum, followed by the hippocampus and posterior neocortex (Sarnat et al. 2010; Huttenlocher and de Courten 1987) and lastly in the frontal cortex, with many of these later phases peaking after birth. In the neocortex the earliest synapses develop between 12 and 14 weeks p/c in the earliest migrating neurons (Tiu et al. 2003; Sarnat et al. 2010), i.e. those that form the preplate, which later splits into the molecular and subplate layers. Abnormalities in both development and pruning of synapses are associated with a variety of neurodevelopmental conditions but these are rarely diagnosed in the fetal period.

Apoptosis is a critical part of brain development and is related to morphogenesis, proliferation and the regulation of progenitor pool size. Apoptosis is an active energy consuming process and in conditions of cerebral energy failure may become inhibited. It is particularly active in areas where rapid structural changes are occurring, where it helps regulate the appropriate size and shape of the structures. Apoptosis plays a particularly important role in the timeline of transient structures and has a different time-course across the regions of the brain. For example, by weeks 6–7 p/c apoptosis is already markedly active in the ventricular zone and preplate (Zecevic and Rakic 2001) and by week 11 p/c has commenced in all cortical layers, although it remains most active in the proliferative zones. Between 12–22 weeks apoptosis has increased significantly throughout the telencephalon; failure of normal apoptosis may lead to lesions with excessive neural parenchyma.
Although developmental brain anomalies are often classified into the putative developmental process disturbed (e.g. proliferation or migration) there are often multiple stages involved in a single patient; for example, disturbances in neuronal proliferation may be followed by disturbed neuronal migration and organisation.

Acquired lesions originating early in development may be difficult to distinguish from primary dysgenesis since a cicatricial response might be lacking. Disorders of brain size may be due to disturbances in cellular proliferation or in apoptosis.

**MICROCEPHALY**

Fetal microcephaly is variably defined as a head circumference >2SD below the mean or below the 3rd centile for gestational age (Table 1.3). There is ongoing controversy about the best standard for diagnosing microcephaly and whether this should be adapted for ethnicity. In addition, fetal centiles may differ from gestational-age adjusted postnatal centiles and fetal head circumference charts are not sex specific. A significant correlation has been described between maternal microcephaly and infant head size at birth (Stoler-Poria et al. 2010). Dominantly inherited microcephaly has a better outcome in some (Dorman 1991) but not all studies (Stoler-Poria et al. 2010) with most based on a postnatal diagnosis. In a substantial proportion of individuals head circumference will improve postnatally (Stoler-Poria et al. 2010).

Infants with a birth head circumference between 2 and 3SD below the mean often have a favourable outcome, especially in the absence of other factors such as brain anomalies (Kurtz et al. 1980) or syndromic conditions. Some studies show that fetal head circumference 2–3SD below the mean for gestational age is not associated with significant differences in intellectual outcome from controls, although behavioural, emotional and executive function impairments are more common (Pilu et al. 1998; Huizink et al. 2003). The latter finding has been ascribed to the higher rate of frontal lobe underdevelopment in these infants (Pilu et al. 1998) or greater maternal psychoaffective stress (Huizink et al. 2003). When birth head circumference falls between 3 and 4SD below the mean the risk of intellectual disability increases to 50% (Dolk 1991) although many still have relatively normal intellectual ability. Once head circumference is more than 4SD below the mean the intellectual outcome is universally poor (Dolk 1991).

The role of overall fetal growth in the outcome of microcephaly is unclear. Fetal growth restriction and a fetal head circumference 2–3SD below the mean increases the risk of learning disabilities. Some studies describe a better outcome for microcephalic newborn infants with normal birthweight (Dolk 1991) while others found no difference between symmetrical or asymmetrical microcephaly (Stoler-Poria et al. 2010).

While microcephaly describes a small head, micrencephaly refers to a small brain. Although head circumference and biparietal diameter are still the primary measures of head size and surrogate for brain size the advent of quantitative fetal MRI (Limperopoulos et al. 2010; Clouchoux et al. 2012b) has better enabled the direct volumetric measurement of the fetal brain parenchyma and is likely to improve prognostication based on brain size in future.

A valuable step in formulating a prognosis for microcephaly is to distinguish primary genetic causes from acquired-destructive forms. Acquired forms often have relatively moderate microcephaly but severe intellectual disability, major neurological abnormalities and often a history of a sentinel event/mecanism. Microcephaly may be accompanied by prominent cerebellar hypoplasia and can be divided into primary microcephaly when there is a known or suspected genetic cause or secondary microcephaly when an insult to the fetal brain results in impaired growth. Attempts at categorising microcephalies based on MRI features have considered the presence of associated cortical thickness, simplified gyral patterns, callosal anomalies, heterotopias and forebrain development (Barkovich and Raybaud 2012). Decreased cortical thickness in microcephaly is suggestive of decreased cellular proliferation and can be seen in in utero infections.

Primary microcephaly (microcephaly vera) is associated with an overall normal brain configuration but neurons in cortical layers II and III are severely depleted. Microcephaly vera is genetically heterogenous with a recessive inheritance (Suri 2003) and MCPH 1–5 gene loci which encode for microcephalin. Markedly hyperkinetic behaviour is common but the neurological examination usually shows very few gross abnormalities and seizures are rare. Intellectual disability is usually mild and most children acquire at least some functional language. Microlissencephaly is an extreme form of microcephaly with a thick cortex and markedly decreased cortical sulci (agyria-pachygyria). Cerebral underdevelopment is especially prominent in the frontal lobes, with cerebellar and brainstem hypoplasia, while enlarged ventricles may be associated. Unlike microcephaly vera microlissencephaly is associated with gross neurological abnormalities, profound intellectual disability and epilepsy.

Radial microbrain is an extreme form of microcephaly where the brain may weigh less than 50 g where radial columns are fairly normal but severely deficient in neurons. Radial microbrain differs from atelencephaly in which there is no cortical structure.
MACROCEPHALY

In the evaluation of fetal macrocephaly the first step is to distinguish between hydrocephalus, space-occupying lesions and megalencephaly, which can usually be achieved fairly reliably by fetal ultrasound, while a family history of macrocephaly with normal outcome is suggestive of dominant familial macrocephaly. Primary megalencephaly may result from abnormalities in neuronal proliferation, migration and organisation and may be syndromic (Sotos syndrome, neurofibromatosis): these conditions are discussed elsewhere in this text.

Hemimegalencephaly (Fig. 1.36) results from unilateral hamartomatous overgrowth of a cerebral hemisphere with associated disturbances of proliferation, migration and differentiation, and an abnormal gyral pattern with pachygyria or polymicrogyria. Ventriculomegaly or ventricular asymmetry is a common referral diagnosis in the fetal period for lesions ultimately diagnosed as hemimegalencephaly. The cerebral cortex in the affected hemisphere is thickened and un laminated with loss of cellular alignment, heterotopias and giant balloon cells. Both the cerebrum and cerebellum may be involved in some individuals: the prognosis is poor and
affected children usually develop severe intellectual disability, hemiparesis and early-onset intractable epilepsy.

**DISORDERS OF NEURONAL MIGRATION**

The successful migration of neurons from distant neuroproliferative zones to their final cortical destination involves the precise orchestration over time and space of signalling guides expressed as gradients of extracellular signals and transcription factors. Neuronal migration disturbances may result from a host of genetic or acquired (disruptive) events across this landscape: the phenotypic expression of disturbances in these complex processes depends on the underlying mechanism, the timing of such and its severity (see also Chapter 3).

Neuronal migration defects have been categorised into a number of different classification schemes that change as new genetic and mechanistic insights emerge. In this chapter on fetal neurology we focus on those lesions that can be diagnosed in utero by current fetal imaging techniques into the following categories (Guerrini and Parrini 2010).

1. **Focal/multifocal neuronal migration defects** which include schizencephaly, mild subcortical band heterotopia and nodular heterotopia.

2. **Diffuse neuronal migration defects** which include lesions in the agyria-pachygyria spectrum such as lissencephaly type 1, severe subcortical band heterotopia and the cobblestone lissencephaly complex (lissencephaly type 2).

Another schema for categorising neuronal migration defects is based on the stage of migration affected and includes four groups. These are lesions originating (1) before (schizencephaly) or at the onset (periventricular nodular heterotopia) of neuronal migration; (2) during the ongoing process of migration (agyria-pachygyria spectrum); (3) from failed penetration of the subplate (lissencephaly with cerebellar hypoplasia) and (4) at the end of migration leading to overmigration (Type 2, cobblestone complex).

**Figure 1.36** Fetal MRI scan showing hemimegalecephaly in (a) axial and (b) coronal planes.

Disrupted signalling in neuronal migration leads to a broad spectrum of neuronal migration defects which can result from failure of neurons to leave the proliferative zone (defective ‘go’ signal), abnormal early detachment from radial glial cells or over-migration (defective ‘stop’ signal) when neurons migrate through gaps in the pial limiting membrane into the subarachnoid space. Each neuronal migration defect reflects specific signalling disturbances. For example, *filamin 1 (FLN1)* is important for cellular locomotion and FLN1 mutations disrupt those signals necessary for postmitotic neurons to leave the ventricular zone, resulting in bilateral periventricular nodular heterotopia (Fox et al. 1998). *Doublecortin (DCX)* is expressed in the leading edges of migrating neurons where it interacts with guidance signals in the extracellular environment. Mutations in DCX, an X-chromosome product, cause band heterotopias in females and lissencephaly in males (X-linked lissencephaly) while mutations of the *LIS1* gene cause heterotopias and/or lissencephaly. Mutations in *LIS1* and *DCX* genes are responsible for 40–75% of type 1 lissencephalies (Dobyns 1989) as well as a milder defect, subcortical laminar heterotopias (Friocourt et al. 2003). Brain lesions associated with the *LIS1* and *DCX* mutations have a fairly typical microscopic picture with a thin outer layer of cells made up of cortical layer 1 and the layers destined to make up cortical layers 5 and 6. This outer band is separated by a cell-sparse layer from a broad underlying layer of cells that became arrested in their migration toward cortical layers 2 and 3 (Forman et al. 2005), while milder forms of *DCX* and *LIS1* mutations may cause band heterotopias. *Reelin (RELN)* is a large glycoprotein molecule secreted by the Cajal-Retzius cells in the outermost cortical (molecular) layer (cortical layer 1) and plays a fundamental role in the columnar and laminar organisation of the cortical cells (Ogawa et al. cortical layer 1). For the migrating waves of neurons destined to populate cortical layers 2–6 in an inside-out sequence reelin plays an essential stopping role once these neurons reach their appropriate cortical location. It also serves an important role in neuronal migration, cortical lamination and positioning.
as well as the polarity of the apical cells. Reelin usually signals the normal detachment of migrating neurons from the radial glial cells; with reelin mutations there is abnormal lamination of a thickened cortex, while marked cerebellar and brainstem hypoplasia are also common. It also appears to have an ongoing stabilising role in maintaining cortical layering (Forster 2014; Frotscher et al. 2009). Certain gene products such as tubulin (TUB) genes encode for alpha and beta tubulins important for neuronal proliferation, migration, neuronal guidance of radial glia, neuronal differentiation and cortical organisation (Ayala et al. 2007). TUB gene mutations are usually sporadic or de novo and associated with a spectrum of dysgenetic brain lesions including neuronal migration disorders, such as lissencephaly and polymicrogyria (Breuss et al. 2012) and posterior fossa anomalies such as cerebellar and pontine hypoplasia, tectal dysplasia and asymmetries of the midbrain and pons (Cushion et al. 2013).

### Focal or Multifocal Neuronal Migration Defects

The principal gene mutations responsible for this class of NMD are DCX, FLN1 and ARFGEF2 (Guerrini and Parrini 2010).

**Schizencephaly** (Figs. 1.30 and 1.37) is a severe but restricted form of neuronal migration defect in which a relatively limited section of the ventricular neuroproliferative zone fails to generate the neuroglial precursors required to populate...
that segment of the cerebral mantle, presumably because of agenesis or destruction of progenitor cells. This results in a cleft extending through the entire cerebral mantle ending in a pial-ependymal seam formed by the apposition of the outermost pial layer and the ventricular ependyma. Grey matter lines the entire cleft although it is abnormal, usually polymicrogyric. These clefts most commonly occur superior to the Sylvian fissure and may be unilateral or bilateral. Schizencephaly is classified into open- and closed-lip types (Figs. 1.30 and 1.37): in open-lip schizencephaly ample CSF is visible along the extent of the cleft while in the closed-lip form CSF is minimal to absent. Up to half of open-lip schizencephaly may later become closed-lipped over time (Nabavizadeh et al. 2014) while in up to 75% of schizencephaly patients the septum pellucidum is absent (Granata et al. 2005) especially when clefts are in the central perisylvian region. Schizencephaly may also be associated with other malformations such as septo-optic dysplasia, ACC and heterotopias.

Open-lipped schizencephaly is complicated by hydrocephalus in up to 50% of patients (Packard et al. 1997). Schizencephaly may be due to genetic mutations such as the homeobox EMX2 gene or acquired lesions early in fetal life (Curry et al. 2005) which are usually vascular or infectious, specifically fetal CMV encephalitis (Iannetti et al. 1998). As schizencephaly originates at the onset of neuronal migration in the third month of gestation it is usually detectable by fetal ultrasound and MRI: the neurodevelopmental outcome for the defect includes mild-moderate intellectual impairment, congenital hemiparesis, macrocephaly and focal seizures.

Heterotopias may take several different forms including periventricular nodular heterotopia, subcortical nodular heterotopia and transmantle heterotopia. Band heterotopia, especially more severe forms, are currently considered a forme fruste of the agryia-pachygyria spectrum although the overlying cortex may be relatively preserved. About 50% of periventricular nodular heterotopia (Fig. 1.38) patients were also affected.
by mutations in the FLNA (filamin-A) gene. Mutations in the ARFGEF2 gene have also been associated with heterotopia: their location may result from failure to migrate from primary proliferative zone or due to excessive proliferation resulting from failure of the stop-signal for proliferation. Heterotopias are often part of more complex malformations: by MRI these lesions appear as nodules of grey matter along the ventricular wall commonly associated with ventriculomegaly. In fact, ventriculomegaly is often the initial referral indication for fetal MRI rather than heterotopia which are not well seen by fetal ultrasound. If isolated and unilateral heterotopia may be asymptomatic or associated with seizures, the latter becoming severe and refractory if presenting early in life (Aghakhani et al. 2005). When these nodules become confluent they may form periventricular band heterotopias (Fig. 1.39) which are genetically heterogeneous XL, AR, and sporadic. Some are transmitted dominantly but primarily in females (Huttenlocher et al. 1994) and an association with vermic hypoplasia and cardiomyopathy has been reported (Parrini et al. 2006). The principal differential diagnosis for these heterotopias is the subependymal hamartomas of tuberous sclerosis; however, by fetal MRI the tuberous hamartomas are not isointense with grey matter and usually iso- or hypointense with white matter. Band heterotopias are the mildest form of agyria-pachygyria lesion and discussed below.

**DIFFUSE NEURONAL MIGRATION DISORDERS**

The lissencephalies: The human fetal brain starts off with a smooth agyric surface which then begins to develop sulci and gyri at specific time-points during gestation. Failure to develop such gyral patterns may be an early sign of a spectrum of neuronal migration disorders called the lissencephaly continuum. There are two major forms of lissencephaly, types 1 and 2 and four less common forms sometimes called variant lissencephaly: these are lissencephaly with cerebellar hypoplasia (LCH), X-linked lissencephaly (XLIS), X-linked lissencephaly with ambiguous genitalia (XLAG) and micro-lissencephaly (Forman et al. 2005). Although both major forms have failure of normal gyral formation they differ fundamentally in the mode of disrupted neuronal migration, with under-migration in type 1 and over-migration in type 2. Specifically, type 1 lissencephaly results when neurons are arrested in their migration prior to their arrival in the appropriate cortical laminae: overall the cerebral wall in type 1 lissencephaly has the appearance of a 12–13 week gestation brain. In Type 2 there is an over-migration of neurons beyond their designated laminae and into the subarachnoid space. As a result the histological features of the cortex are completely different, although both forms have failure of normal gyral development and thickened cerebral cortex. In type 1 a more superficial cellular layer has poorly aligned/oriented cells and the deeper cell layer has arrested ectopic neurons while in type 2 lissencephaly the cortex has no recognisable organisation, with large clusters of heterotopic neurons and no lamination. Protruding out onto the surface of the brain are nodules of neural tissue made up of neurons that have migrated through the pial lining, giving a cobblestone appearance.

**Lissencephaly Type 1**

Figure 1.40 is part of an agyria-pachygyria spectrum with varying degrees of absent sulcal-gyral formation. The gene mutations associated with this spectrum are LIS1 (AR) and DCX (X-linked), although ARX, TUBA1A and RELN mutations are also known to be associated, with dysregulation of microtubular function the common underlying mechanism for disturbed neuronal migration in these conditions (Francis et al. 2006). Any lesion along this spectrum may be associated with mutation of either LIS1 or DCX, however type 1 lissencephalies are most commonly associated with LIS1 mutations while DCX mutations are more common in subcortical band heterotopia. More than half of classic lissencephaly patients have mutations of the LIS1 gene on chromosome 17 and about 25% have mutations in DCX or XLIS (on the X chromosome). All known genetic causes of type 1 lissencephaly have a thickened cortex but important differences exist in the topography and histopathology (Forman et al. 2005). Mutations in LIS1 and DCX have a different topography of lissencephalic cortex, being more severe posteriorly with LIS1 mutations and more severe anteriorly with DCX mutations. Classic type 1 lissencephaly due to LIS1 mutation results in a small brain with tortuous surface vessels, the cortical lesion having a broad swath of neurons prematurely arrested in their migration causing a thickened, usually 4-layered ‘cortex’ overlying a thin ribbon of white...
matter, with olivary nuclei ectopic and dentate nuclei abnormally convoluted. On fetal MRI classic lissencephaly shows a very thick smooth cortex with shallow sylvian fissures and an axial figure-of-eight shape to the cerebrum. LIS1 mutations are associated with two clinical syndromes, classic type 1 lissencephaly (isolated lissencephaly sequence; ILS) and the Miller-Dieker syndrome. Isolated lissencephaly sequence is not associated with other major brain or extracerebral anomalies, with callosal agenesis uncommon. In Miller-Dieker syndrome – which forms a minority of type I lissencephaly – additional dysmorphic facial features are present, including a narrow forehead, upturned nostrils, long upper lip, digital abnormalities and retinal hypervascularisation. Miller-Dieker syndrome is associated with codeletion of LIS1 and YHAWAE, a contiguous gene (Cardoso et al. 2003), possibly explaining the broader dysmorphic phenotype: most LIS1 mutations are de novo. The prognosis of both forms of type 1 lissencephaly is bleak with severe intellectual disability, diffuse atonic weakness and microcephaly, which is usually mild, while life expectancy is reduced.

In addition to type 1 lissencephaly TUBA1A mutations result in microcephaly, spastic cerebral palsy (CP) and intellectual disability (Bahi-Buisson et al. 2008).

The pachygyria phenotype (Fig. 1.41) is milder than lissencephaly and the thickened cortex having abnormally broad gyri. Pachygyria occurs in several different syndromes, with most individuals affected as a result of sporadic mutations of the LIS1 gene: congenital CMV encephalopathy may resemble this phenotype.

The majority of individuals affected by subcortical band heterotopia (Fig. 1.42) are girls, as a result of mutation of the sex-linked DCX gene that codes for doublecortin. Expression is highly variable as the superficial cortex in subcortical band heterotopia may appear normal or mildly abnormal with shallow sulci. The cortex is separated by a narrow strip of white matter from a thick band of grey matter whose border with the overlying white matter is smooth: in girls the band may range from thick and diffuse to thin and localised. Compared to LIS1 lissencephaly the band of arrested neurons is thinner and the cortex thicker with a more advanced gyral pattern. Seizures and cognitive impairment are frequent complications although occasional patients appear to develop normally: some have found an inverse relationship between the thickness of the subcortical band and cognitive level (Barkovich et al. 1994).

X-linked lissencephaly (XLIS) results from a DCX mutation. In males with XLIS the lissencephaly resembles that in LIS1 but has a frontal predominance (Dobyns et al. 1999) while
Lissencephaly Type 2

In type 2 lissencephaly the cortex is moderately thickened with irregular surfaces at both the pial aspect and interface with the subcortical white matter, which leaves the cortical surface with a cobblestone appearance and little to no overlying subarachnoid space (Fig. 1.43). The white matter is decreased in volume and dysmyelinated while severe cerebellar dysplasia (PMG) with cysts and brainstem hypoplasia may be present. Unlike type 1 lissencephaly in which neuronal migration is prematurely arrested type 2 lissencephaly results when deficient ‘stop signals’ cause over-migration beyond the pial-glial limiting membrane forming neuroglial ectopia into the subarachnoid space. In type 2 lissencephaly disturbances in tangential migration may also play a role (Kato and Dobyns 2005; Marcorelles et al. 2010). About two-thirds of type 2 lissencephaly patients have evidence of an α-dystroglycanopathy related to a defect of O-glycosylation of the extracellular matrix proteins. Mesenchymal signalling is important for normal development of the underlying fetal brain, evident in cerebral malformations that result from developmental defects in the overlying pial basement membrane. The outer surface of the brain is normally covered by a glia limitans which is in turn covered by the pial basement membrane. In the cerebellum the astrocytic end-feet are those of the Bergman glia and in the cerebral, the radial glial cells. Leptominges around the cerebellum are critical for the proliferation and migration of granule cells in the external granular layer and for normal CBM lamination (Wang and Zoghbi 2001). Inadequate fusion between the pial basement membrane and the footplates of the radial glial cells results in disorders of neuronal migration and premature radial glial apoptosis. In the remaining 30% of patients no genetic cause is currently known.

Three subtypes of alpha-dystroglycanopathy have been described (Devisse et al. 2012), namely the Walker–Warburg syndrome, Fukuyama disease and muscle-eye-brain disease. The association between muscle, eye and brain lesions results from common abnormalities in the basement membranes of the pia limitans and muscle fibres, resulting in defective attachment of radial glial cells and contractile muscle proteins to the basement membranes, while similar binding defects may occur in the retina. A number of gene mutations have been associated with these conditions: merosin deficiency is one cause of abnormal basement membrane attachment and results in the merosin-deficient congenital muscular dystrophy group of disorders which is in turn associated with a spectrum of brain anomalies including microcephaly, leukoencephalopathy, neuronal migration defects and cerebellar lesions including hypoplasia and cyst formation (van der Knaap et al. 1997; Triki et al. 2003). Although infants with type 2 lissencephaly occasionally have normal eyes, muscle involvement is usually inevitable and has the appearance of severe muscular dystrophy.
Walker–Warburg syndrome

Walker-Warburg syndrome (Fig. 1.43) has a striking phenotype with profound anomalies of the brain and eyes, enabling diagnosis in the fetal period. Inheritance is usually autosomal recessive due to a mutation of the POMT1 gene. It is the most severe of the muscle-eye-brain syndromes, with most patients showing no developmental progress before they die, usually in the first year of life. The cortex is thick and often double-layered with complete disorganisation due to subcortical heterotopic islands, with the overlying meninges often thick and opaque, with few sulci detectable. Hydrocephalus is common usually due to the thickened meninges, decreased extra-axial CSF spaces or aqueductal stenosis. Hydrocephalus further obliterates the extra-axial fluid, while the pyramidal tracts and corpus callosum may be absent with an encephalocele present. The cerebellum is small with an absent vermis; as with other conditions in this spectrum the white matter is severely under-myelinated. Striking posterior fossa anomalies may be present including pontine hypoplasia, thickened midbrain tectum with fused colliculi and abnormal Z-shaped kinking of the thin brainstem with marked cerebellar hypo/dysplasia. Ocular anomalies include microphthalmia, glaucoma with intra-ocular haemorrhages and colobomas.

Fukuyama disease

Fukuyama congenital muscular dystrophy is an autosomal recessive disorder due to a mutation in the fukutin (FTCD) gene. The resulting fukutin deficiency may result in disruption of the pial-glial limitans and muscle disease dominates the postnatal clinical picture: in Japan this is the most common form of congenital muscular dystrophy. There is a broad range in severity of brain findings in Fukuyama’s congenital muscular dystrophy but in general the phenotype is milder than that of Walker-Warburg syndrome. The cobblestone lissencephaly is less severe with hydrocephalus, callosal dysgenesis and encephalocoeles uncommon: consequently, the diagnosis is less easily made by fetal imaging. Delayed sulcation and subcortical cerebellar cysts may be the only clues on fetal imaging.

Muscle-Eye-Brain disease

Muscle-Eye-Brain disease is associated with a number of gene mutations. Early in infancy severe hypotonia is present but by late childhood marked spasticity has developed as well as severe cognitive impairment and epilepsy. The cortex is markedly abnormal resembling polymicrogyria with delayed myelination and widely dilated ventricles which may be hydrocephalic in origin. Fetal imaging may show a small ventral pons with a cleft and a large often rounded tectum as well as cerebellar cysts.

Disorders of Cortical Organisation

Polymicrogyria (Fig. 1.44) is a cortical malformation that has origin during the period from late neuronal migration into
the phase of cortical organisation. The gross appearance of the cortex is one of many excessively small and shallow folds giving a ‘pebbled’ appearance. Macroscopically the cortex may appear to be thickened but this appearance is due to overfolding, evident on microscopy in which the cortex typically shows loss of neurons with greater or lesser loss of lamination and the appearance of fused molecular layers in the folds. Polymicrogyria has been categorised by some as layered or unlayered: layered (classic) polymicrogyria, has four distinct cortical layers and is thought to be postmigrational in origin. Patients often have gliotic changes and laminar neuronal necrosis suggesting an insult occurring after completion of migration (Toiti et al. 1998). Unlayered polymicrogyria is thought to originate from disturbances in the terminal phases of migration, resulting in a poorly laminated cortex with disorganised heterotopic neurons, often arranged in columns descending into the subcortical white matter. Several different forms are described but central to all is disorganisation of the normal six-layered cortex and abnormal sulcation. The regional distribution of polymicrogyria is varied but the sylvian fissure is involved in the majority of patients. The syndrome of bilateral perisylvian polymicrogyria (developmental Foix-Chavany-Marie syndrome) (Graff-Radford et al. 1986) is associated with dysphagia and dystarsia (a pseudobulbar palsy), seizures and cognitive impairment, as well as motor deficits including arthrogryposis (Gropman et al. 1997). Polymicrogyria often occurs in association with other dysgenetic lesions including schizencephaly, callosal agenesis and cerebellar hypoplasia: this form of brain anomaly may be seen after acquired lesions such as congenital CMV infection and ischaemic lesions (Barkovich et al. 1995). The features of polymicrogyria on fetal MRI may be relatively subtle: the cortical irregularity may be best seen on the inner surface of the cortex at the underlying white matter interface rather than on the outer surface. The extent of neurodevelopmental impairment in these infants is related to the extent and topography of the polymicrogyria, aetiology and presence of associated cerebral anomalies or syndromic features.

**Other disorders of cortical organisation:** A number of more localised or focal cortical anomalies are known but these are seldom detected by fetal imaging and therefore not discussed here.

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**FUNCTIONAL DEVELOPMENT OF THE FETAL BRAIN**

Functional and structural development of the fetal brain are intimately connected. Three aspects of functional development of the fetal brain are discussed here, namely (1) electrochemical development; (2) development of cerebral energy metabolism and vasoregulation; and (3) the behavioural expression of fetal brain development.

**Electrochemical Development**

Two central processes are essential for electrochemical development of the fetal brain. These are (1) development of efficient, stable synapses under both excitatory and inhibitory control and (2) development of behaviourally relevant and sensory driven electrical activity from an earlier system of primitive endogenous discharges. Early neurotransmitter systems differ significantly from those in the mature brain, with neurons able to communicate through activation of membrane receptors early in development before these receptors are organised into synapses. Gamma amino-butyric acid (GABA)-ergic synapses and networks develop before glutamatergic synapses and in contrast to a later role, GABA is initially excitatory and responsible for all cerebral excitatory activity. This early excitatory action of GABA results because the early resting chloride gradients across the neuronal membranes are reversed. Therefore, opening of chloride channels by GABA during early development is depolising (excitatory) as opposed to the later hyperpolarising inhibitory action. Early GABA release is tonic and non-vascular, diffusing to distant neurons and acting in a paracrine manner. Neurotransmitter clearance from the synaptic cleft is slow in the immature brain because re-uptake channels are lacking. Together these features result in a primitive pattern of gross, non-discrete neural activity, generating very large spontaneous currents that manifest as major discharges called giant depolarising potentials (GDP) or spontaneous activity transients (SAT). Spontaneous bursts of discontinuous activity are a fundamental feature of the developing nervous system and are active before sensory systems become functional (Pallas 2001; et al. 2006). Although these massive electrical discharges convey little if any information they are a key stimulus for early neuronal development (Vanhatalo and Kaila 2006), providing critical trophic support for neuronal survival: deprivation of such activity leads to apoptotic cell death (Blankenship and Feller 2010; Colonnese and Khazipov 2012). These endogenous discharges are also important for early synapse development and the fundamental construction of activity-dependent wiring and functional neural networks (Khazipov and Luhmann 2006; Tolner et al. 2012): this early endogenously driven brain activity is independent of external sensory input (Bourgeois et al. 1989; Colonnese and Khazipov 2012). Later, with the transition of GABA to an inhibitory role and the development of the interneuronal inhibitory system, spontaneous discharges decrease and disappear.
Development of connections between the sensory experience of the environment and developing cortex is the pivotal step in subsequent development of the nervous system. The epigenetic experiential sculpting of discrete, sensory-driven and behaviourally relevant neural activity is dependent on a number of systems becoming aligned. Linkage between the environment and cortex constitutes the pivotal developmental switch required for epigenetic influences on brain development. First, neural connectivity must be established between sensory receptors and the developing cortex. Efficient synaptic systems must develop that are under both excitatory and inhibitory control, with functional neurotransmitter re-uptake channels at the synaptic cleft. Only under these conditions can organised and topical communication between neurons occur and lead to the development of neuronal circuitry.

Electrical discharges are increasingly triggered by glutamatergic pyramidal neurons with development of the glutamate neurotransmitter system. During the early phases of glutamatergic system development GABA-ergic neurons play a permissive or facilitatory role in the activation of glutamatergic discharges. Central to the development of a behaviourally relevant nervous system is the switch in GABA activity from excitatory to inhibitory, with this switch occurring when chloride pumps become more efficient and mediate a fall in intracellular chloride. Hereafter, inhibitory GABA acts in concert with excitatory glutamate at discrete synapses to enrich the efficacy of synaptic function.

The first synaptic activity develops among the neurons that were first to migrate, namely the preplate neurons which become split into the molecular and subplate layers. The precise onset of spontaneous electrocortical activity in the human fetal brain is unclear but in preterm infants scalp EEG recordings show alternating bursts of activity and quiescence from around 24 weeks of gestation (Hellström-Westas et al. 1991; Klebermass et al. 2006). Whether the time course and development of these EEG patterns in the preterm infant are similar to those in the gestational age-equivalent fetus remains unclear. Modulation of these SAT by peripheral sensory stimulation acting through thalamocortical connections plays a putative role in the linking of the subplate to the cortex at around 28 weeks gestation (Price et al. 2006). Hereafter, the SAT evolve through several stages, increasing initially over the sensory cortices after which they generalise. At ~30 weeks gestational age interhemispheric synchrony of the SAT is inconsistent and might be mediated by brainstem centres. After 34 weeks gestational age increasing SAT synchrony develops as callosal connectivity, while in animals there is also intermittent activity at the brainstem level which may contribute to the synchrony, as evidenced by the coherence developing between heart rate variability and SATs in humans (Vanhatalo and Kaila 2006; Pfurtscheller et al. 2005): these discontinuous patterns become increasingly more continuous with maturation (Dreyfus-Brisac 1962; Lombroso 1985). Continuous activity becomes more established around term gestation as the thalamocortical fibres make their final cortical connections.

With development of inhibitory interneuronal circuits within the cortex higher frequency continuous multifrequency electrocortical activity develops. Such higher frequency activity in the beta and theta range is now known to be essential for ongoing development of cortical function (Buzsaki and Draguhn 2004; Steriade, 2006; Palva et al. 2005). SATs persist until term after which they may be pathological: the coupling of SAT bursts to changes in cerebral oxygenation suggest they are energy-dependent (Roche-Labarbe et al. 2007).

Cerebral Energetic and Vasoregulatory Development

Normal development of the fetal brain is critically dependent on an oxygen substrate supply capable of supporting the energy demands of the complex structural and functional maturation processes. Consequently, oxygen substrate deprivation is an important cause of fetal brain lesions, ranging from destructive injury to developmental disruption or subterritorial disturbances in programming.

Development of the fetal brain circulation: At 4 weeks p/c, after the neural tube closes, a primordial system of endothelium-lined vascular channels is in place and by the end of the first trimester the cerebral hemispheres are covered by an extensive mesh of leptomeningeal arteries. Subsequent cerebral vascular development is tightly coupled to regional parenchymal maturation. Arterial development is largely complete in the brainstem and cerebellum by 24 weeks gestation and in the basal ganglia and diencephalon by 28 weeks. During the third trimester rapid development of the cerebral hemispheres, in particular the cortex, is associated with major changes in the hemispheric vasculature. From the original simple vascular plexus extensive anastomoses develop covering the cerebral surface. Large penetrator arteries develop at the base of the brain to supply the basal ganglia, diencephalon and periventricular germinal matrix. From the cerebral convexity thinner penetrating vessels descend into the hemispheres: by 24 weeks of gestation, when the major phase of cerebral neuronal migration has been completed, these thin penetrators extend from the pial surface into the periventricular regions. Between 24 and 28 weeks shorter penetrators rapidly develop to support the period of intense cortical organisation, axonal outgrowth and synapse formation. Cerebral vascular density increases during gestation (Ballabh et al. 2004): angiogenesis increases rapidly in the cerebral cortex after 26 weeks and by 35 weeks has reached adult levels of vessel density and diameter (Mito et al. 1991).

Energy metabolism in the immature brain: Cerebral energy metabolism in the human fetus remains poorly understood largely because of inaccessibility to available measurement techniques. Current knowledge is limited to inferences from animal studies and studies of the preterm born human (Kinnala et al. 1996; Powers et al. 1998; Altman et al. 1993; Altman et al. 1988) both sources with questionable applicability to the human fetus. A number of factors have perpetuated the misperception that anaerobic glycolysis is the major...
energy source for fetal cerebral metabolism. First, the fetus is hypoxemic in terms of both circulating free and bound oxygen with the partial pressure of oxygen in the umbilical vein (28–35mmHg) and artery (16–28mmHg) being significantly lower than in the postnatal circulation. At the same time the fetus has an oxygen demand two-fold that of an adult. Second, earlier studies suggested that energy synthesis through mitochondrial oxidative phosphorylation was less efficient in the immature brain (Murthy and Rappoport 1963). Third, the immature fetal brain is uniquely capable of using alternative energy substrates such as lactate and ketones during periods of glucose limitation (Stanley et al. 1979). However access to these alternative energy sources is but one part of a system of compensatory mechanisms (see below) to protect the immature brain during energy deprivation: although the immature brain is capable of using these alternative energy substrates (Hellman et al. 1982) aerobic glucose metabolism (with little or no lactate production) provides the principal energy support for the developing fetal brain. In fact, at no stage of fetal brain development is anaerobic glycolysis alone capable of meeting all energy requirements: although cerebral energy demand starts off low in early fetal life it escalates rapidly during the third trimester to support the function of enzymes such as Na/K-ATPase which are critical for maintaining electrocortical activity and the propagation of action potentials. With these escalating cerebral energy demands there is a concurrent increase in the number and functional capacity of cerebral mitochondria with increasingly efficient energy production (Murthy and Rappoport 1963).

A system of compensatory mechanisms maintains cerebral oxygen metabolism in the fetus. The fetus has an intrinsic system of compensatory mechanisms that enables it to tolerate moderate oxygen deprivation. This system coordinates responses mediated by a series of rapid neurally mediated cardiovascular reflexes and slower endocrine and behavioural responses aimed at both increasing oxygen/substrate supply to critical organs and decreasing oxygen metabolism. In fact, these fetal compensatory mechanisms normally maintain the fetus in a state of oxygen surplus (Martin, 2008; Bennet et al. 2003): understanding of these fetal responses to hypoxemia is based largely on animal models, primarily fetal sheep and to a lesser extent from the preterm infant (or ex utero fetus). Fetal cardiovascular and metabolic autoregulatory systems are sufficiently developed even early in development to buffer against hypoxia for surprisingly long durations with little or no injury (Gunn et al. 2001; Gunn and Bennet 2008; Bennet et al. 2003). In fetal sheep adaptive circulatory responses to moderate hypoxemia can be maintained for prolonged periods as long as metabolic acidosis does not develop (Bocking et al. 1992; Richardson et al. 1989; Rurak et al. 1990a; Rurak et al. 1990b). In fact, in these animals global and cerebral oxygen metabolism fails only when the circulating pH falls below 7.0. In this manner intrapartum uterine contractions, which result in sharp decreases in maternal arterial supply of the placenta (Janbu and Neshem, 1987) and therefore in repeated mild hypoxemia, are normally well tolerated (Modanlou et al. 1974; Huch et al. 1977; Wiberg et al. 2006).

During hypoxemia the fetus activates several endogenous compensatory responses to preserve fetal oxygen metabolism in critical tissues (including the heart and brain) by decreasing energy utilisation and increasing substrate supply (Boddy et al. 1974; Natale et al. 1981; Bocking and Harding 1986; Richardson, 1992; Richardson et al. 1992; Giussani et al. 1993). Initially, tissue oxygen delivery can be maintained by increasing oxygen extraction but when umbilical venous oxygen content falls below 50% of normal a series of hemodynamic responses is activated, known as circulatory centralisation (Wladimiroff et al. 1986) or brain sparing. These responses are mediated by neural (mainly adrenergic), circulating (catecholamines, serotonin, and angiotensin-II) and local mechanisms (e.g. nitric oxide, prostaglandins). Changes include increased shunting of oxygenated umbilical venous return...
across the ductus venosus (Jensen et al. 1991; Bristow et al. 1983) and foramen ovale, as well as into the cerebral and coronary circulations (Peeters et al. 1979). In the systemic circulation hypoxemia triggers chemoreceptors which then activate a series of autonomic responses: these include a vagally mediated bradycardia (to decrease myocardial energy demand) and peripheral vasoconstriction to increase blood pressure mediated by neural and circulatory adrenergic stimulation (Peeters et al. 1979; Richardson et al. 1996). Maturation of fetal responses to hypoxia has been best studied in ovine models, in which a moderate hypoxic insult elicits little or no fetal heart rate changes before 0.7 of gestation. Hereafter, hypoxemia triggers an initial bradycardia followed by mild tachycardia, a response that becomes increasingly robust over the remainder of pregnancy (Iwamoto et al. 1989; Matsuda et al. 1992; Fletcher et al. 2006). Although this sequential response to hypoxemia is interpreted as the emergence of autonomically mediated responses to hypoxia at 0.7 of gestation, coincident with maturation of neurohormonal regulators and chemoreceptor function (Hanson 1997; Jensen 1996), it might also reflect the increasing oxygen demand toward the end of gestation (Shelley 1961; Szymonowicz et al. 1988; Wassink et al. 2007).

Hypoxia-activated chemoreceptors are known to be functional in the normal fetus (Bennet et al. 2003) (Bartelds et al. 1993; Jensen and Hanson 1995) however, fetal reflex responses to hypoxia differ in several ways from the adult. For example, in the hypoxic fetus, rapidly acting, neurally mediated chemoreflexes suppress fetal breathing movements (Moore et al. 1989) and fetal heart rate: these cardiac decelerations are vagally mediated and presumably serve to decrease cardiac energy metabolism (Fletcher et al. 2006). The decrease in fetal heart rate reduces the cardiac output and blood pressure triggering sympathetically mediated vasoconstriction. This in turn restores blood pressure and diverts more oxygenated blood flow to the heart, adrenals and brain. If hypoxemia persists the slower activation of endocrine and paracrine endo-thelial responses follows (Martin 2008; Bennet et al. 2003): if hypoxemia remains moderate an accumulation of circulating catecholamines causes a gradual tachycardia, presumably to improve cardiac output. In this manner the moderately hypoxaemic fetus is able to maintain normal oxygen delivery to vital organs for long periods of time (Bennet et al. 1998; Richardson et al. 1993).

Although most, if not all, intrinsic cerebral vasoregulatory (or autoregulatory) systems begin to develop during the fetal period, their efficiency is related to the maturational level of the fetus (Bilger and Nehlig 1993). During fetal hypoxemia there is not only a global increase in cerebral blood flow but also a redistribution of cerebral perfusion preferentially to those brain regions developing most actively at that particular gestational age (Cavazzuti and Duffy 1982). Initially the fetal brainstem has a particularly robust vasodilatory response; toward term this capacity develops in the thalamus and basal ganglia as well as regions of the cortex (Tolcos et al. 2003). If hypoxemia is sustained oxygen utilisation in the fetal brain is actively suppressed, ‘powering down’ neuronal activity, slowing the EEG and decreasing fetal movements. The adenosine triphosphate (ATP) breakdown product, adenosine, accumulates during hypoxia and plays a prominent role in the cerebral cellular and vascular responses to sustained hypoxia. Specifically, adenosine activates vascular A2 receptors causing regional cerebral vasodilation, increasing perfusion and oxygen delivery (Blood et al. 2002). Adenosine also stimulates presynaptic A1 receptors inhibiting synaptic transmission and decreasing cerebral metabolism and oxygen demand (Blood et al. 2003).

In chronic hypoxic conditions cerebral cellular metabolism is downregulated and there is an increased production and secretion of vascular growth factors, including vascular endothelial growth factor (VEGF) (Martin et al. 1998) and hypoxia-inducible factors (HIF) (LaManna et al. 1992) leading to increased capillary density.

DEVELOPMENT OF FETAL MOVEMENTS AND BEHAVIOUR

The study of fetal movements goes back to observations made almost two centuries ago on aborted fetuses. In 1837 Erbkam described his observations of fetal movements after spontaneous miscarriages (Erbkam 1837). In the 1930s the Pittsburgh anatomist Davenport Hooker studied and filmed the activity of human fetuses from clinically indicated surgical abortions (Wilson 2014). For many years there was debate about whether these fetal movements were spontaneous or evoked, such as in 1952 when Hooker proposed that fetal movement was ‘a spontaneous reflex for which the stimulus is not yet known’ (Wilson 2014). More recently our understanding of the maturational trajectory of fetal activity and behaviour has accelerated for several reasons. First, the advances in survival of increasingly preterm infants has provided a window on these evolving patterns. Second, advances in fetal imaging, both ultrasound and more recently MRI, have allowed the characterisation of spontaneous and reflex fetal movements, behavioural patterns and state changes (de Vries and Fong 2006). Fetal motor activity starts early and develops into a complex repertoire of movements and behavioural states. Fetal movements depend on the gestational age and amount of intraterine space available: these are therefore more pronounced in younger fetuses and polyhydramnios.

Fetal movements start at 7 weeks p/c as slow sideways bending of the fetal axis, coincident with the rapid development of synapses in the cervical cord. Breathing movements, initially irregular, are seen with movement of the diaphragm from around 8 to 12 weeks p/c and reflect cervical origin of the phrenic nerve. By 8–10 p/c weeks whole body movements, including the trunk and extremities, develop and may be either fast, explosive startles or slower, more complex movements (‘general movements’) (Prechtl et al. 1979) that include rotation. General movements are fluent, becoming increasingly complex and variable in speed and range until the late second–early third trimester, after which they decrease as term
approaches: general movements persist until around 20 weeks postnatal when they are gradually replaced by purposeful movements. Manual exploration of the face with occasional thumb sucking is common between 14 and 20 weeks, decreasing thereafter. In the neurologically abnormal fetus these general movements become abrupt, fragmented, monotonous and repetitive, often more forceful and of greater amplitude. The initial simple movement patterns originate from spontaneous discharges in the spinal and brainstem circuits. With development of descending, especially inhibitory, pathways from higher brain centres these spinal–brainstem activities become modulated into more complex and variable movements. Progressive organisation into complex and distinct behavioural patterns, reactivity and habituation to stimuli denotes supraspinal modulation of endogenous spinal–brainstem activity.

Around 20 weeks gestational age fetal activity becomes diurnal with peak movements in the evening accompanied by a diurnal variation in fetal heart rate. Fetal behaviours develop a periodic nature after midgestation in which periods of activity and quiescence alternate (Nijhuis et al. 1982; de Vries et al. 1985). Early diaphragmatic activity begins with frequent fetal hiccups that subsequently evolve to more rhythmic respiratory movements (Pillai and James 1990.) Over time the breathing movements become increasingly influenced by emerging behavioural states, diurnal variation, maternal glucose, hyperoxia and carbon dioxide levels (Baier et al. 1990). Breathing movements tend to be decreased in abnormal conditions like maternal substance abuse, smoking, oligohydramnios and fetal hypoxia. As term approaches fetal breathing movements normally decrease markedly.

By 28 weeks of gestation the topographic organisation of neural connections, particularly at the thalamocortical level, begins to allow the emergence of goal-directed behaviours. Such cerebral modulation of fetal behaviour can be demonstrated by the development of habituation to repeated stimuli. From around 36 weeks of gestation fetal behavioural states emerge, characterised by combinations of behavioural conditions that remain stable for periods of time. In addition, between 34–38 weeks of gestation major kicking movements decrease and are replaced by lower amplitude coordinated movements.

Fetal behavioural states begin to emerge toward the end of the second trimester, initially consisting of quiet sleep (rapid eye movements and mouthing) and active sleep (clusters of movements). The active awake state has a high level of kicking and a high heart rate.

**Placental Function**

**Placental development and support of the fetal brain**

An understanding of normal placental development and function is important for the understanding fetal brain development. Likewise, many of the acquired brain lesions in the fetus directly or indirectly involve the placenta. The placenta contains tissue of both fetal and maternal origin and is perfused by two circulations, the maternal uteroplacental circulation and the fetoplacental circulation. The main functional units of the placenta where most of the fetal-maternal exchange occurs are the terminal branches of the chorionic villi (Fig. 1.46), comprised of an outer syncytiotrophoblast layer (in direct contact with the maternal blood), an inner cytotrophoblast layer, a basement membrane and the endothelial cells of the fetal vessels. Nutrients, therefore, must cross from the syncytiotrophoblast through the fetal capillary endothelium to reach the fetal circulation. In these terminal villi the fetal and maternal (in the intervillous space) circulations are separated by a single tissue layer several cells thick, making them in essence functionally distinct (Wilkening et al. 1982). Although the primary determinant of fetal growth is placental nutrient transport the placenta has numerous other functions: these include anchoring the conceptus and integrating the embryo/fetus with the maternal circulation, suppressing immune rejection by the maternal system, synthesis of endocrine/growth factors, excreting waste products and epigenetic programming.

After implantation at 1 week post-conception the trophoblast develops into a multinucleated syncytiotrophoblast and mononucleated trophoblast. The trophoblast in turn develops down two pathways, the villous and extravillous trophoblast, both essential for successful implantation and placentation. The villous trophoblast is responsible for oxygen-nutrient transport and endocrine function while the extravillous trophoblast establishes the placental circulation by invading the endometrium and inner third of the myometrium, transforming the maternal spiral arteries by breaking down the muscularis and remodelling the endothelium. In so doing the autonomic and local vasomotor responsiveness is lost, transforming the uteroplacental circulation into a dilated low resistance and poorly contractile system that is essentially pressure passive to the maternal systemic circulation. The lacunae between the syncytiotrophoblast and the decidua form the intervillous spaces will be perfused by maternal blood.

The relationship between oxygen and normal fetal/placental development remains complex, in part due to the maturational changes in fetal antioxidant systems. During placental development there is a delicate balance between pro- and antioxidant forces, when both low and high oxygen levels may impair placental development. At the same time reactive oxygen species also play an important role as second messenger systems in many normal signalling pathways and serve as critical intermediates of multiple homeostatic systems. During the first trimester a low oxygen environment is essential for normal placental implantation and development as well as for normal fetal organogenesis, angiogenesis and cell proliferation (Ottoesen et al. 2006): higher placental oxygen levels during the first trimester result in miscarriage and teratogenicity. Secretions of the endometrial glands provide early support of the fetoplacental unit and maternal circulatory support is not established until the end of the first trimester. At the start of the second trimester fetal growth accelerates with greater
demand for placental transport and protein synthesis. This is particularly true of the brain with rapid increase in mass, resulting from development of synaptic, dendritic and axonal elements in the cortical and subcortical grey matter. Concurrently there is an abrupt ‘oxygen transition’ with a three-fold increase in the fetoplacental oxygen content, together with a surge in antioxidant enzyme synthesis (Schneider 2011). After midgestation both placental circulations show an exponential increase in perfusion which occurs by different mechanisms. The uteroplacental blood flow increases up to five-fold as remodeling of uterine resistance vessels converts it into a high capacitance circulation while fetoplacental blood flow increases primarily through proliferation of arterioles in the terminal villi resulting in a low resistance system with a large surface area (Stuart et al. 1980; Trudinger et al. 1985). Fetoplacental vessels lack autonomic innervation with vasoregulation depending on local or circulating vasoactive substances (46–50) (Kiserud and Acharya 2004), such as the vasoconstrictors angiotensin-II, endothelin and prostanoids (54) and the vasodilator, nitric oxide. Catecholamines have minimal effect on the fetoplacental circulation: consequently the surge in catecholamines during fetal hypoxemia causes significant vasoconstriction in the fetal peripheral circulation but not in the fetoplacental, myocardial or cerebral circulations.

Transporter function, both nutritional and excretory, develops in the placenta utilising both active and passive transport systems. Nutrient transfer occurs by simple (e.g. glucose) or facilitated diffusion (e.g. amino acids) with placental functions regulated by an array of signals and channels. Insulin growth factors (especially IGF-1) are important regulators of placental nutrient transport. Glucose transport is strongly influenced by maternal glucose levels, the process being facilitated by at least six glucose transporters. Amino acid transport occurs through as many as 20 different transporters and results in fetal amino acid levels higher than maternal. Maternal lipoproteins are taken up by placental lipoprotein receptors.

In addition to transferring maternal molecules to the fetus the placenta is also able to synthesise critical substrates for brain development. The endocrine and metabolic roles of the placenta are complex. Hormones (hCG, hPL, oestrogen and progesterone) and growth factors are secreted by the syncytial layer of the chorionic villi and released into both the maternal and fetal circulations. Fetal brain synthesis of neurosteroids, potent agonists of GABA-A receptors, is particularly important for brain development and dependent on precursors produced by the placenta. One such neurosteroid is allopregnanolone, the levels of which are markedly elevated in the fetal brain particularly during the third trimester when it is thought to increase sleep in the normal fetus through a tonic suppression of fetal behavioural state. In animal models allopregnanolone increases sharply with acute hypoxic stress and acts as a neuroprotectant reducing apoptotic cell death especially in the hippocampus.

![Figure 1.46 Anatomy of the normal placenta](https://www.biog1445.org/demo/07/ovaryplacenta.html).
Around midgestation the placenta can synthesise serotonin (5-HT) from maternal substrates (Bonnin et al. 2011): 5-HT plays an important role in neuronal proliferation and axonal outgrowth at this time. The placental source of 5-HT is provided primarily to the forebrain in animal models. Deprivation of this source of 5-HT might underlie some of the emotional and psychiatric outcomes in patients affected by placental failure.

The normal placenta provides important barrier functions to a host of hazardous influences. Maternal stress has an increasingly apparent adverse impact on the developing fetus and especially the fetal brain (Bale et al. 2010) while excess exposure to catecholamines and glucocorticoids is harmful to the developing fetus (Meyer 1985). Two placental systems normally act as a functional placental barrier against maternal and fetal stress, namely the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) and norepinephrine transporter (NET). Glucocorticoids, which are normally important for fetal growth and development, have adverse fetal consequences when produced in excess (Hahn et al. 1999). The normal placenta regulates fetal glucocorticoid exposure through the enzyme 11β-HSD-2 (Krozowski et al. 1995) which inactivates cortisol to inert cortisone. Placental 11β-HSD-2 production increases with fetal maturation (Murphy and Clifton 2003) but both expression and activity are decreased by factors such as hypoxia, nutritional deprivation and sustained maternal stress. In placental failure attenuation of 11β-HSD-2 activity exposes the fetus to elevated levels of corticosteroids and leads to fetal growth restriction and programming for later disease.

The human placenta expresses norepinephrine transporters (NET) (Ramamoorthy et al. 1993) and other neurotransmitter transporters (Hayer-Zillgen et al. 2002). The fetus has a high production rate of catecholamines and placental catecholamine clearance is an important homeostatic function of the placenta (Bzoskie et al. 1995). Norepinephrine is a major catecholamine released during pregnancy, with the placental NET responsible for specific reuptake and fast termination of norepinephrine’s action after neuronal release: elevated norepinephrine levels may downregulate the placental expression of 11β-HSD-2 (Sarkar et al. 2001). Sustained high levels of norepinephrine may overrule the NET system, resulting in downregulation of placental 11β-HSD-2 and increased fetal exposure to cortisol. Blood levels of norepinephrine are particularly high in conditions such as pre-eclampsia (Manyonda et al. 1998) possibly because of a decrease in NET (Bottalico et al. 2004). In conditions of placental dysfunction decreases in NET may result in high norepinephrine levels and be associated with vasoconstriction (Bottalico et al. 2004) including in the umbilical vein.

The placenta serves other critical barrier functions including suppression of immune rejection of fetal tissue as well as a barrier against viruses, inflammation and autoimmune processes. The immune functions of the placenta are complicated but include immunological suppression of rejection as well as selective transfer of immune function to the fetus. For example, Immunoglobulin G (IgG) is transferred from the maternal circulation to the fetus by 20–24 weeks while IgM transfer is blocked.

**ACQUIRED ENVIRONMENTAL INFLUENCES ON THE FETAL BRAIN**

The structural consequences of an insult to the developing brain are dependent not only on the nature and dose of the insult but also maturational timing. Maturational timing matters because the developing brain has specific periods of critical development and vulnerability, when an insult might have enhanced effects. A critical period is a unique and limited time window during which a specific developmental event must occur, with failure to do so having significant and permanent repercussions. A vulnerable period during normal development occurs when the fetal brain is particularly exposed to specific insults or when fetal defenses are lacking. Since critical periods often have increased cerebral energy demands they become vulnerable periods for insults involving cerebral energy deprivation. Intrauterine insults may elicit a broad range of responses in the fetal brain, with a corresponding wide range in the nature and emergence of clinical manifestations. The latency to onset of clinical manifestations following a fetal brain insult may extend across the lifespan and depends largely on the severity, developmental timing and chronicity of the fetal insult.

After mid-gestation, when cerebral energy substrate demands escalate, a system of compensatory mechanisms (discussed above) develops in the cerebral circulation that buffers the developing brain against transient perturbations in energy supply. Consequently, the fetal brain develops the capacity to respond to insult with a graded response. Low-intensity insults that are brief may trigger effective compensatory (homeostatic) responses that dampen or nullify the insult: these have brief adaptive value but no enduring effect on brain development or function. With more sustained chronic or repetitive low-level insults the fetus may successfully maintain trajectory of brain development through compensatory mechanisms (homeorhesis) that come at a cost, such as activation of epigenetic programming that results in later-emerging consequences such as autism and schizophrenia. More severe but non-destructive insults may cause obvious structural disruptions in brain development, sometimes grossly indistinguishable from primary dysgenetic lesions. Finally, severe insults, especially during critical/vulnerable periods, may be destructive with fetal demise or an obvious fetal/neonatal encephalopathy and features of injury on brain imaging. In summary, the response of the fetal brain to insult depends on the pathway through which the immature brain channels the insult, i.e. adaptive, disruptive or destructive. There are currently no techniques for distinguishing the insult thresholds responsible for activation of adaptive, homeorhetic, disruptive or destructive processes (Gluckman et al. 2005).

In the next section we consider important examples of insults to the fetal brain in the context of their maternal, placental or fetal origin.
Fetal Brain Insults of Maternal Origin

Changes in the maternal environment may result in changes in placental function with effects on the fetus (Bale et al. 2010). The primary mechanism is through changes in the expression of placental transporters that regulate the transfer of glucose, amino acids and vitamins. Maternal endocrine substances including glucocorticoids, insulin growth factors, insulin and leptin serve as intermediaries to effecting these changes.

**Maternal diabetes mellitus:** It has been known for some time that exposure to maternal hyperglycemia may have adverse effects on fetal organ development and function (Freinkel 1980). Gestational and pregestational diabetes mellitus complicate between 5–15% of all pregnancies, with the former usually developing during the third trimester after major organogenesis is complete. Conversely, pregestational diabetes mellitus, types 1 or 2, may result in periconceptional hyperglycemia if poorly controlled, with adverse consequences (Balsells et al. 2009). In fact, about 10% of infants born to pregestational diabetic mothers of either type have evidence of birth defects involving blastogenesis in the first 4 weeks post-conception. Higher levels of maternal haemoglobin A1c, a marker for poor glycemic control, have been positively associated with increasing rates of birth defects. The developing human nervous system is especially vulnerable to hyperglycemia, resulting in 15-fold increase in neurological malformations including anencephaly, holoprosencephaly and syntencephaly as well as neural tube defects and the caudal regression syndrome (Farrell et al. 2002; Salbaum and Kappen 2011). Gestational diabetes on the other hand only slightly increases the rate of major malformations but significantly increases the risk of perinatal neurological complications resulting from macrosomia (obstructed labour, perinatal asphyxia and brachial plexus palsy) and glucose metabolic derangement (Castori 2013). In addition to these major disruptive and destructive lesions children born to diabetic mothers are at increased risk for neurodevelopmental anomalies including impaired motor function, attentional issues, intellectual impairment and learning disabilities, as well as later schizophrenia (Van Lieshout and Voruganti 2008; Isohanni et al. 2001; Cannon et al. 2002; Kim-Cohen et al. 2003). A recent large retrospective study found that gestational diabetes mellitus diagnosed before 26 weeks gestation (but not pre-existing type 2 diabetes) was a significant independent predictor of subsequent autism in the offspring (Xiang et al. 2015).

There are likely to be several mechanisms underlying these neurological consequences of diabetes in the fetus. Hyperglycemia may activate a cascade of events that include chronic tissue hypoxia, oxidative stress and inflammation (Philips et al. 1984; Georgieff 2006). Poorly controlled maternal diabetes mellitus increases oxidative stress because hyperglycemia depletes antioxidants and increases the generation of reactive oxygen species (Li et al. 2013). Oxidative stress alters placental endothelial function including nitric oxide and adenosine pathways which are critical to vasoregulation in the non-innervated placental circulation (Guzman-Gutierrez et al. 2014). Hyperglycemia also reduces fetal iron levels which may in turn disturb cortical development especially in hippocampal structure and function (Deregner et al. 2000; Siddappa et al. 2004) as well as development of monoaminergic neurotransmitter systems (Beard et al. 2006; Lozoff and Georgieff 2006). Chronic tissue hypoxia is likely to be triggered by chronic elevated insulin levels which increases fetal oxygen metabolism beyond that which the placenta is able to sustain: in addition, maternal diabetes may be associated with vascuopathy resulting in fetal growth restriction (Moore 1997).

**Maternal malnutrition**

For many years the primary focus of nutritional management of pregnancy was on the prevention of maternal nutritional deprivation. Classic studies (Barker and Clark 1997) of maternal starvation during the Dutch famine of 1944–45 and other disasters has formed the basis for understanding the role of epigenetic disorders in developmental programming that lead to chronic disorders such as later obesity, the metabolic
syndrome and diabetes as well as neurological sequelae such as schizophrenia (Geddes et al. 1999; Eide et al. 2013), attention deficit disorder, and autism (Fattal-Valevski et al. 1999). The effects of maternal malnutrition on fetal brain development are mediated in part by decreased levels of 11β-HSD-2 and elevated fetal cortisol exposure. Animal studies suggest that during acute maternal nutritional deprivation a catabolic gene expression programme is activated in the placenta and under such conditions the placenta itself may be catabolised to provide critical energy and accretion substrate to the developing fetus (Broad and Keverne 2011) including critical structural substrates for development of the hypothalamus.

In contrast to nutritional deprivation obesity has become the number one public health issue in the United States almost one-third of women in the reproductive age group are now obese (Hedley et al. 2004), meaning that the adverse fetal effects of maternal obesity are increasingly recognised.

Specific nutritional deficiencies such as folic acid and iron deficiency (Georgieff 2008) have been associated with specific neurological conditions and are discussed in greater detail elsewhere. Maternal folic acid deficiency is associated with neural tube defects, with folic acid a form of vitamin B9 and essential for multiple functions including fetal and placental growth. This has led to recommendations from the Food and Drug Association and the Centres for Disease Control in the United States for folic acid fortification of flour and folate supplementation for all women capable of pregnancy. Estimates of a reduction in neural tube defects since these recommendations have ranged from 26–50% although this number remains controversial: the picture may be clouded by a concomitant increase in obesity in recent years and the known association with neural tube defects (Ray et al. 2005).

**Exogenous Maternal Insults**

Several commonly prescribed medications may be associated with structural anomalies in fetal nervous system development. Alcohol intake during pregnancy may cause a complete or partial form of fetal alcohol syndrome which includes fetal growth restriction, microcephaly, specific facial anomalies as well as long-term neurodevelopmental impairments: there also appears to be a dose–effect relationship with no clear safe threshold. Since many of these children have few if any structural anomalies but clear alcohol-related neurobehavioural disorders (ARND; ‘behavioural teratogenesis’) the diagnosis has now been expanded to fetal alcohol spectrum disorders (FASD). Cocaine, a presynaptic blocker of monoaminergic neurotransmitter (dopamine, norepinephrine and serotonin) reuptake, causes elevated circulating catecholamine levels with elevated sympathetic tone which may particularly marked in the fetus (Padbury et al. 1986). Cocaine may interfere with multiple steps in normal brain development from neuronal proliferation to migration and cortical connectivity (Gressens et al. 1992). In addition, the destructive ischaemic and haemorrhagic brain lesions seen in some cocaine-exposed fetuses may result from the vasoconstrictive effects of cocaine. Through catecholaminergic effects cocaine may have the same generic effect as other forms of fetal stress (such as fetal growth restriction) which alters fetal developmental programming through epigenetic mechanisms. Cocaine down-regulates norepinephrine transporter (NET) in the placenta (Bzoskie et al. 1997) increasing circulating norepinephrine in the fetus, thereby downregulating 11β-HSD-2 (see above) and causing a chronic state of fetal hyper-cortisolism. Long-term follow-up of children exposed to cocaine in utero have shown a significantly lower burden of major neurodevelopmental disability than once feared (Frank et al. 2001); however follow-up studies have shown less striking but more prevalent disturbances in arousal, behavioural regulation and attention. These disturbances in behavioural regulation and executive function appear to be the major long-term consequences of prenatal cocaine exposure (Lester and Lagasse 2010). Methamphetamine has become the premier drug of abuse in many parts of the world. Like cocaine effects are largely mediated by increased catecholamine activity through excessive release of dopamine and serotonin and inhibition of monoamine re-uptake. The consequences of prenatal methamphetamine exposure are less well known but their effect on catecholamine metabolism would predict adverse effects on the development of neural connectivity. Methamphetamine is also known to have vasoconstrictive effects and in animal models causes a decrease in uteroplacental perfusion and fetal hypoxia (Stek et al. 1995). As with other drugs of abuse, polypharmacy and associated socioeconomic factors complicate the clear delineation of long-term methamphetamine effects on the fetal nervous system. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications for the more than half-million pregnant women with major depressive symptoms in the United States each year. SSRIs block the re-uptake of serotonin (5HT) by binding to the serotonin transporter, increasing circulating 5HT. With the growing understanding of the role played by serotonin in normal brain development there has been widespread concern for the long-term neurodevelopmental effects of these agents. Recent reports have not shown an increased risk of malformations after fetal SSRI exposure (Rahimi et al. 2006) although earlier studies did suggest an increase in cardiac malformations and pulmonary hypertension (Chambers et al. 1996): the vasoconstrictor effects of 5HT might underlie the transient decrease in uterine artery blood flow in animal models (Morrison et al. 2002). During the early postnatal period these infants may present with excessive irritability, tremors, insomnia, poor feeding and abnormal posturing (Kallen 2004): this behavioural phenotype is transient but the long-term outcome of these infants is unclear.

**Fetal Infections**

The impact of intrauterine infections and more specifically fetal encephalitis on long-term neurological outcome, including deafness and visual impairment, has been recognised for
some time. Some agents such as congenital rubella have been reduced to largely historical interest in countries with effective immunisation programmes but remain a problem in the developing world. With the advent of effective antiretroviral agents the maternal-fetal transmission of HIV has been significantly reduced (Read 2010). The rate of varicella developing in pregnant women ranges from <1 to 3 per 1000 and very few (<2%) deliver infants with congenital infections. Conversely, other agents such as lymphocytic choriomeningitis virus (LCMV) have been recognised only recently as hazards for the fetal brain. Although neonatal herpes simplex encephalitis is a devastating and potentially treatable disease with an incidence ranging from 0.025 to 0.3 per 1000 live births the vast majority of these are acquired during the birth process, with only 5–10% representing congenital infections (Kimberlin 2004).

The vast majority of congenital infections are acquired through the maternal circulation and placenta where infection may lead to placental inflammation, vasculitis and placental insufficiency, with risks of fetal demise, miscarriage and intrauterine growth restriction. Despite improved fetal imaging the majority of congenital CNS infections are detected in the neonatal period when the infant displays non-specific features such as jaundice, hepatosplenomegaly, rash, intrauterine growth retardation, microcephaly, hydrocephalus or chorioretinitis, some of which are not accessible during the fetal period. The neurologist may become involved when fetal imaging studies detect cerebral anomalies or more general fetal growth restriction. Features common to congenital encephalitis infections include periventricular hyperechogenicities, intracranial calcifications, cystic encephalomalacia, hydrocephalus or ex vacuo ventriculomegaly and periventricular leukomalacia. The structural effects and neurodevelopmental consequences of congenital encephalitis are determined by multiple factors including the infectious agent and the associated specific cellular tropism, maternal immunity and the timing of maternal infection. Less well understood are the genetically regulated factors that determine the maternal or fetal response to the infectious agent.

Broadly speaking, the imaging features of fetal encephalitis can be categorised as destructive or disruptive, often occurring in combination. Features of a destructive process include tissue loss, parenchymal calcifications and haemorrhage. Calcifications may occur in regions of cellular necrosis as a result of direct viral cytotoxicity or vasculitis and are especially common in areas of rapid neuronal proliferation such as the periventricular regions. Disruptive lesions may closely resemble primary dysgenetic lesions and unless there are associated destructive lesions the distinction may be difficult. Although disruptive lesions such as cortical dysplasia, schizencephaly or polymicrogyria are likely to result from an interaction between the infection-inflammation and the underlying genetic programme the precise pathogenesis remains unclear. Intriguing similarities between the imaging and neuropathological features of congenital viral infections (especially CMV and LCMV) and rare familial disorders such as pseudoTORCH syndromes (Briggs et al. 2008; Abdel-Salam et al. 2008) suggest that much remains to be learned about the interplay of virus infections and the genes that determine the complex patterns of neural development.

Cytomegalovirus (Fig. 1.47) has become the most commonly recognised cause of fetal viral infection in most developed countries. During primary maternal infection the fetal transmission rate is around 50%. The rate of congenital infection by CMV in the United States and Europe is around 0.6% of all newborn infants, and of these about 20% will manifest symptoms either at birth (10%) or develop long-term sequelae such as hearing loss, cognitive deficits or motor impairment (Istas et al. 1995). Humans are the natural host and only reservoir for CMV affecting humans and transmission...
is the result of direct contact through infected saliva, urine, semen or cervical secretions. Most maternal primary CMV infections are asymptomatic and if symptoms develop they may range from mild flu-like illness to a mononucleosis syndrome. Vertical transmission can occur at any time during gestation but the risk is highest during the first half of this period. Women who are seropositive for CMV pre-conceptually are less likely than seronegative women to give birth to infants with congenital CMV disease (Fowler et al. 2003). Specifically, pre-existing maternal immunity confers significant but not full protection against fetal transmission. Fetal transmission may still occur in about 1% of patients affected by fetal transmission through reactivation of the maternal infection (Stagno et al. 1982) or infection with a different strain of CMV (Boppana et al. 2001).

The diagnosis of fetal CMV encephalitis should be considered in patients affected by fetal microcephaly with specific fetal neuroimaging signs. Intracranial calcifications on antenatal US are a common presentation and present in about 50% of congenital CMV patients. Other imaging abnormalities associated with congenital CMV encephalitis include hydranencephaly and cerebral cortical malformations such as polymicrogyria, schizencephaly, pachygyria/lissencephaly and cortical dysplasia (Bale et al. 1985; Hayward et al. 1991) findings that suggest infection prior to the 20th week of gestation. Congenital CMV infection is commonly associated with cerebellar hypoplasia.

Differential Diagnosis: A number of fetal infections are associated with intracranial calcifications; however, the calcifications in congenital CMV are usually in a periventricular distribution. Although brain parenchymal calcifications in congenital toxoplasmosis (see below) tend to be more diffuse, scattered this pattern can also be seen in CMV or LCM virus infections (Bonthius et al. 2007; Bale et al. 1985); the cerebral and cerebellar lesions in congenital CMV and LCMV may also be indistinguishable (Wright et al. 1997; Bonthius et al. 2007; Bale et al. 1985; Hayward et al. 1991). Congenital HSV infections may be associated with calcifications that typically involve the thalamus and basal ganglia (Hutto et al. 1987).

Diagnosis: If the pregnant mother is seropositive for CMV-specific IgM it is important to perform a CMV IgG avidity test. If the CMV IgG avidity is low it suggests an acute or recent infection. Avidity remains low for about 18–20 weeks after infection and if low before 18 weeks gestation the sensitivity for predicting a pregnancy at risk is very high (Lazzarotto et al. 2000). Conversely, if maternal CMV-specific IgG avidity is high during the first 12–16 weeks of pregnancy then there is low risk of fetal transmission. Amniotic fluid CMV polymerase chain reaction (PCR) testing has high sensitivity and specificity; however, the threshold viral load predictive of symptomatic fetal infection is not known. If the amniotic fluid CMV PCR is negative fetal infection is unlikely. While culture of CMV from the saliva or urine of an infant during the first three weeks of life remains the criterion standard for the diagnosis of congenital CMV disease congenital infection is established by detection of CMV-specific IgM in the serum of the infant or CMV nucleic acids in urine or saliva using PCR. Where fetal infection is suspected postnatal confirmation must be made within three weeks of birth.

Prognosis: Survivors of congenital CMV are at high risk of a broad spectrum of long-term, often debilitating neurodevelopmental sequelae including CP deafness, visual dysfunction, epilepsy and developmental delay/intellectual disability. Unsurprisingly, CMV encephalitis with earlier onset, which tends to be associated with neuronal migration defects, and those with intracranial calcifications are more likely to have severe adverse neurodevelopmental sequelae (Noyola et al. 2001). The acute neonatal presentation of this condition, including systemic abnormalities such as hepatosplenomegaly, thrombocytopenia and anemia, is discussed further in the section on neonatal neurology. Prior to the availability of ganciclovir about 80% of infants with symptomatic congenital CMV infections had permanent disability attributable to CMV infection (Pass et al. 1980) with at least 50% developing sensorineural hearing loss (unilateral or bilateral, mild to profound) and 10–20% developing chorioretinitis. In fact, CMV is currently the most common non-genetic cause of permanent hearing loss among children living in the United States and is responsible for 20–25% of all children suffering from hearing loss (Grosse et al. 2008; Fowler et al. 1997). A late onset form of progressive or fluctuating sensorineural hearing loss may develop in children with congenital CMV disease, even among infants without symptomatic CMV infection in the neonatal period (Fowler et al. 1997; Grosse et al. 2008). Epilepsy, often presenting as infantile spasms in the first year, may develop, especially with disruptions in brain development.

Treatment: Postnatal ganciclovir is likely to reduce the risk of permanent deafness but its effect on other neurodevelopmental outcomes remains uncertain. The development of an effective vaccine for eliminating congenital CMV disease has been remarkably slow. Furthermore, recent data suggesting the larger role for non-primary maternal infection makes the efficacy of vaccination questionable. At present neither the ACOG nor CDC recommend universal maternal screening for seropositivity for several reasons. First, maternal serosensitivity does not rule out fetal infection: in the United States about two-thirds of patients with congenital CMV and the vast majority in resource-limited settings are born to women with preconceptional seropositivity (Manicklal et al. 2013; Wang et al. 2011), presumably because of reactivation or primary infection with a different CMV strain. Second, diagnosis of fetal infection does not predict symptomatic disease or sequelae. Third, there is no preventive therapy currently established, with antenatal treatment options limited: ganciclovir cannot be used during pregnancy because of mutagenicity. Early phase data from an non-randomised study of intravenous CMV hyperimmunoglobulin in pregnant women with CMV positive amniotic fluid (Nigro et al. 2005) suggested a significant benefit. However, a subsequent
Stage 2 randomised clinical trial failed to replicate these results, possibly because it was underpowered (Revello et al. 2014). The results of two Phase 3 randomised clinical trials currently being performed in the United States and Europe are awaited, while the efficacy of intrapartum hyperimmune IgG as a potential treatment to prevent transmission of CMV from mother to fetus remains unresolved. Postnatal therapy with ganciclovir for 6 weeks is associated with improved hearing outcomes in congenitally infected infants (Kimberlin et al. 2003). Valganciclovir is a pro-drug of ganciclovir which is rapidly converted to ganciclovir on absorption and reduces the fetal viral load (Kimberlin et al. 2015). In the infected newborn infant it appears to deliver more reliable and consistent blood levels of ganciclovir than does the intravenous form. Several modifications to the current standard protocol for postnatal treatment are under consideration and discussed in more detail in Chapter 11 on Infectious Diseases.

Congenital Toxoplasmosis (Fig. 1.48) is currently the second most commonly recognised congenital infection but is approximately 10-fold less common than congenital CMV. *Toxoplasma gondii* is a ubiquitous protozoal parasite known to infect mammals, especially felines (domestic cats) and birds. Human infection occurs through ingestion of food (usually meats) contaminated by the cysts or oocysts. Maternal symptoms may be mild or absent but if present the most common presentation is lymphadenopathy sometimes with fever, resembling infectious mononucleosis. The rate of congenital infection ranges from 0.1–1.0/1000 live births, being particularly high in France. The majority of infected infants do not show symptoms at birth, with infection blood-borne from the mother to the placenta where an infection is set up and from where the parasite enters the fetal circulation. Transmission to the fetus is dependent on the timing of maternal infection during pregnancy. If maternal infection occurs during the first 10 weeks of pregnancy the rate of fetal infection is very low. After 15 weeks gestation the transmission rate rises rapidly and may be as high as 80% if the mother becomes infected in the last weeks of pregnancy. Conversely, the risk of severe congenital infection is highest between 10 and 24 weeks gestation, decreasing to term when the overall risk of infection is high but the severity mild. The net result of these opposing trends in incidence and severity is that the highest risk for early symptomatic congenital infection occurs when the mother seroconverts between 24 and 30 weeks of gestation (Dunn et al. 1999). Congenital toxoplasmosis is complicated by chorioretinitis in around 75% of infants and approximately 10% develop sensorineural hearing loss (compare to congenital CMV above) (Swisher et al. 1994). Major fetal growth restriction and preterm birth are uncommon, in unlike congenital CMV. Unlike CMV Toxoplasmosis does not cause disruptions in fetal brain development, the neuropathology being mediated solely by inflammation and tissue destruction, including that caused by vasculitic thrombosis. The meningoencephalitis is often striking and multifocal, granulomatous in nature, with ocular involvement including microphthalmia and retinal scars that may resemble colobomas. Microcephaly is less common than in congenital CMV but when present implies major cerebral tissue destruction. Unlike congenital CMV macrocephaly, usually indicating hydrocephalus, commonly accompanies congenital toxoplasmosis. Intracranial calcifications are scattered throughout the brain with no regional predilection in most patients: some individuals show a basal ganglia and periventricular predominance. Calcifications may be nodular or curvilinear and a combination of the two is highly suggestive of toxoplasmosis: at autopsy the most
common neuropathology finding is extensive parenchymal necrosis as a result of vascular involvement. These lesions are most concentrated in the cortex and basal ganglia where they may be cystic and calcified. Periventricular and periaqueductal vasculitis, leading to thrombosis and necrosis, is typical of toxoplasmosis. Lesions may rupture into the ventricular system where the high protein deposition and ependymitis (especially around the aqueduct) predispose to hydrocephalus. In some patients hydrocephalus due to aqueductal stenosis may be the only finding.

Diagnostic testing: The standard initial screening test is maternal serology for elevated toxoplasma-specific IgM. These titers may remain high for long periods and so ideally seroconversion or a rising titre can be demonstrated, while tests of IgG avidity are also helpful: diagnosis can be made rapidly by amniotic fluid PCR with a sensitivity of 80%. Postnatally, histological examination of the placenta will demonstrate the parasites.

Management: Shunting of obstructive hydrocephalus and extended courses of antitoxoplasma therapy using pyrimethamine and sulfadiazine may have a striking beneficial effect on the outcome of infants with congenital toxoplasmosis (Guerina et al. 1994; McLeod et al. 2006). In the pretreatment era more than 50% of infants with congenital toxoplasmosis developed long-term sequelae. Since the advent of postnatal treatment with pyrimethamine/sulfadiazine most infants with congenital toxoplasmosis have favourable outcomes with low risk of sensorineural hearing loss or new eye lesions due to T. gondii recrudescence (46).

Lymphocytic choriomeningitis virus (LCMV) is a rodent-borne arenavirus virus endemic in wild mice, the primary vector. Humans become infected through contact with infected aerosols or fomites (Sheinbergas 1976; Wright et al. 1997; Barton and Mets 2001): between 5–10% of adults in the United States are seropositive for LCMV (Bonthius et al. 2007). Although the incidence of congenital infection is presumed low congenital LCMV encephalitis is an under-recognised cause of fetal encephalitis (Bonthius, 2012; Anderson et al. 2014). The primary maternal infection is typically a mild-moderate ‘flu-like syndrome’ and most mothers of children with congenital LCMV recall an episode of fever, myalgias, malaise, pneumonitis and sometimes later an aseptic meningitic picture. The fetal infection is acquired vertically during the primary maternal infection, either transplacentally or less commonly, during birth. The effects in the fetus tend to be severe with miscarriages and fetal demise: the postnatal mortality exceeds one-third among pregnancy survivors. The LCMV is highly and selectively neurotrophic during the fetal period, especially to neuroblasts in the periventricular germinal matrices where it impairs the normally neuroproliferative activity and subsequent neuronal migration (Bonthius et al. 2002, 2007). The virus may also elicit a pronounced host-mediated inflammatory response with destructive changes resulting in subsequent areas of periventricular calcification and cysts (Fig. 1.49). Fetal LCMV infection affects only the brain and eyes causing often severe microcephaly, hydrocephalus and chorioretinitis (Wright et al. 1997; Bonthius et al. 2007). Chorioretinitis occurs in >90% of congenital LCMV infections while deafness is rare: obstructive hydrocephalus and macrocephaly may develop postnatally in infants with congenital LCMV infections (Larsen et al.
1993), even in those born microcephalic. Congenital LCMV encephalitis causes cerebral and cerebellar atrophy (Fig. 1.49a) and neuronal migration disturbances, while fetal intracranial haemorrhage has also been reported (Anderson et al. 2014). As with other fetal insults the long-term manifestations are related to the gestational age at which the fetal infection is acquired (critical periods).

**Diagnosis:** Differentiating congenital LCMV encephalitis from that due to congenital toxoplasmosis and CMV infections may be difficult, however, the infection has several distinguishing features. Specifically, congenital LCMV infection has few if any significant extraneural findings with fetal growth restriction, rash, hepatosplenomegaly and thrombocytopenia rare: hydrops fetalis has been reported in several confirmed cases of fetal LCMV (Anderson et al. 2014; Meritet et al. 2009) with hearing loss uncommon but chorioretinitis virtually universal. The most sensitive test for recent maternal infection is an ELISA test for LCMV IgG and IGM, performed at the CDC (Lehmann-Grube et al. 1979; Enders et al. 1999). Amniocentesis with PCR testing for LCMV mRNA is useful but only during the period of viral shedding in the fetus (Cordey et al. 2011).

**Treatment:** No vaccine has been developed to date: ribavirin has been used to treat postnatal patients with variable success and with significant toxicity risk. Lavipiravir is an agent that has shown promise in cell culture studies but has not undergone clinical trial.

**Zika Virus Associated Microcephaly**

In 2015 an epidemic of Zika virus was reported in Central America and the Caribbean with some infants of infected mothers reported to have severe microcephaly (Mlakar et al. 2016; Fig. 1.50). Zika virus is an emerging mosquito-borne flavivirus originally isolated from monkeys in the Zika forest in Uganda in 1947. Many infected individuals have been reported in the Pacific Islands, Brazil and other areas of South America (Brasil et al. 2016). The infection causes dengue-like fever symptoms including fever, headache, arthralgia, myalgia and a maculopapular rash in adults,
while infants of infected mothers have been reported with microcephaly at birth (Hazin et al. 2016). One carefully evaluated individual was a 25-year-old young woman who had fever and rash at the end of the first trimester of pregnancy: a fetal ultrasound at 29 weeks revealed microcephaly with calcifications in the fetal brain and placenta. After the mother requested termination of pregnancy a fetal autopsy revealed micrencephaly with complete agyria, multifocal dystrophic calcifications in the cortex and subcortical white matter and mild focal inflammation. The Zika virus was found in the fetal brain using reverse transcriptase-polymerase chain reaction (RT-PCR) and electron microscopy. Epidemiological evidence suggests that Zika virus associated microcephaly is emerging as a very important cause of fetal microcephaly in fetuses whose mothers live in or travel to areas where the Zika virus is endemic. A recent paper demonstrated that the Zika virus can infect human embryonic cortical neural progenitor cells in the laboratory, providing a potential mechanism by which the virus can damage the fetal brain (Tang et al. 2016).

**Fetal Brain Insults of Placental Origin**

The placenta has many different normal functions (discussed above), all of which are at risk when placental failure develops. The placenta is critical to fetal brain development from many different perspectives, including endocrine and growth factor trophic support, however the vast majority of work to date has focused on failure of placental respiratory function and nutrient supply, which forms the major focus in the section below.

**Placental Respiratory Failure**

Limitation of placental gas exchange by any mechanism may progress to placental respiratory failure or fetal asphyxia as evidenced by fetal hypoxemia and acidosis. Broadly speaking, potential mechanisms for placental respiratory failure may range from decreased uteroplacental perfusion and/or oxygenation, increased diffusion distance at the villous membrane, decreased maternal-fetal circulatory interface, decreased fetal oxygen carrying capacity (e.g. fetal anemia) and fetal circulatory anomalies. The fetus has a multifaceted system of compensatory responses (discussed above) activated by hypoxemia, however, these temporizing responses are limited and eventually overwhelmed when hypoxemia becomes too severe, prolonged or repetitive (Mallard et al. 1992; Gunn et al. 1992). The threshold for fetal decompensation to hypoxemia can be breached by several different pathways, however, a common final pathway is the development of fetal acidemia and haemodynamic compromise. When lactic acidosis reaches a critical threshold a cascade of events unfolds setting up the perfect storm for fetal brain injury. Specifically, circulating lactic acidosis paralyses catecholaminergic peripheral vasoconstriction, causes myocardial dysfunction and abolishes cerebral autoregulation.

**Placental Ischaemic Disease**

The term placental ischaemic disease includes fetal growth restriction (FGR), placental abruption and pre-eclampsia. These conditions have a common causal origin, i.e. failure of normal placentalation due to impaired trophoblast invasion. All three conditions also have a significantly increased rate of fetal and neonatal mortality and brain injury and long-term neurodevelopmental sequelae in survivors. Both placental abruption and pre-eclampsia may be complicated by FGR and the rate of adverse neurodevelopmental outcome increases for both these conditions when the fetus is also growth restricted (Ananth 2014). In placental ischaemic disease the risk of brain injury from impaired placental function is further compounded by the significant risk of preterm birth and associated brain injury. In addition to spontaneous preterm birth the increased risk of fetal demise in all three of these conditions has increased the frequency of elective preterm delivery. In fact, these three forms of placental ischaemic disease together form the leading cause of preterm birth, accounting for well over half of preterm deliveries (Ananth and Vintzileos 2006): consequently, preterm birth related brain insults are likely to play an important role in the neurodevelopmental morbidity seen in survivors of placental ischaemic disease.

**Pre-eclampsia** is defined as the onset of hypertension, often rapidly progressive, and proteinuria after 20 weeks gestation in women without previous hypertension and proteinuria. Pre-eclampsia complicates at least 5–8% of all pregnancies worldwide, a number two-fold higher in developing countries (Sibai et al. 2005; Maynard et al. 2008). It is usually a disease of first pregnancy and other risks include in the antiphospholipid antibody syndrome (nine-fold increased risk), previous pre-eclampsia (five-fold increased risk) and diabetes (3-fold increased risk). Although the pathophysiology of pre-eclampsia remains poorly understood it is generally agreed a key step along the causative pathway is placental oxidative stress with the generation of pro-inflammatory cytokines and/or angiogenic factors that activate maternal endothelial cells. The fundamental mechanism of impaired fetal growth in pre-eclampsia is most likely fluctuating oxygenation rather than hypoxia alone: this in turn is mediated by deficient trophoblast invasion, with incomplete de-muscularisation of the spiral arteries leaving them susceptible to vasoactive influences. Consequently spontaneous constrictrions in spiral arteries occur with fluctuations in uteroplacental flow generating oxidative bursts into the placental circulation.

**Fetal growth restriction** (FGR) is broadly defined as failure of a fetus to achieve its inherent growth potential; however, it is difficult to establish this potential in the individual fetus. Consequently there have been multiple attempts to identify the best predictive measure. The first criterion currently used to diagnose FGR is an estimated fetal weight below the 10th centile. This definition identifies the small-for-gestational age (SGA) fetus which might be associated with a heterogeneous group of conditions including chromosomal anomalies, infection, maternal substance abuse, toxins, malnutrition and...
constitutional small size. To establish the diagnosis of placental-based FGR additional criteria beyond SGA must to be satisfied, including a fall-off in estimated fetal weight over time and/or other evidence of placental failure such as Doppler features of increased placental vascular resistance. It is well known from earlier studies using cord blood sampling that placenta-based FGR fetuses are at significant risk for hypoxemia, hypoglycemia, hypercapnea and acidosis, compared to normally growing fetuses (Soothill 1987; Economides 1991). The fundamental defect in FGR is reduction in terminal villous volume and surface area, a process that can start as early as the end of the first trimester. Similar to pre-eclampsia (another cause of FGR) trophoblast invasion is deficient (but less so than in pre-eclampsia) with abnormal plugging of the spiral arteries. Spiral arteries in the FGR placenta are not sufficiently converted to the normal gestational pattern with large terminal caliber and loss of the muscularis layer. Consequently, these spiral arteries retain excessive vasoreactivity during periods of fluctuating oxygen tension such as during placental oxygen transition (see above) at the end of the first trimester. Such fluctuations in oxygenation generate bursts of reactive oxygen species that enter the intervillous space where they cause membrane and microvascular injury with villous regression, loss of surface area and increased resistance to umbilical arterial flow. This in turn leads to a decrease in the proportion of fetal blood that perfuses the placenta, leading to fetal hypoxemia.

Placenta-based FGR results in a multisystem fetal syndrome. There appear to be at least two forms of placental-based FGR based on the gestational age at which they present. Preterm (early onset) FGR is much less common and starts in the second trimester, is more rapidly progressive and typically results in elective delivery or fetal demise by 34 weeks gestation. Preterm FGR is a progressive vascular condition characterised by distinct changes in placental resistance as evidenced by reduced, absent or reversed end diastolic flow on Doppler measurements in the umbilical artery. Late-onset FGR has onset after 34 weeks gestation and has a more heterogeneous aetiology and histopathology. Placental resistance changes are much less florid by Doppler than in preterm FGR: consequently, reliable Doppler biomarkers are not available to guide management of late-onset FGR.

Preterm FGR is far better studied and understood than late-onset FGR. Abnormalities in placentation are prominent, especially in the FGR that complicates pre-eclampsia. The progressive process starts with abnormal adaptation of the spiral arteries of the uteroplacental circulation which then progresses through oxidative stress affecting the terminal villi of the fetoplacental circulation where a combination of ongoing ischaemia, thrombosis and endothelial injury causes an increasing loss of these critical exchange units, with an increase in placental vascular resistance and fetal hypoxemia. The initial signs of this increased fetoplacental resistance are detected by increased resistance to diastolic flow in the umbilical artery and subsequent changes can be viewed as phases of fetal compensation and decompensation. During the compensatory phase there is a progressive decrease in resistance in the cerebral circulation as placental (and hence descending aorta) resistance increases, resulting in periods of retrograde deoxygenated flow across the aortic isthmus and into the cerebral perfusion (Fouron et al. 1999; 2009): the compensation phase does not seem to have significant short-term consequences. With further progression the limit of fetal haemodynamic compensation is reached, heralding the pre-terminal phase of decompensation. During this phase metabolic acidosis, myocardial failure and multisystem organ failure develop, with fetal demise becoming imminent. Cardiac decompensation can be detected by abnormal Doppler waveforms that emerge in the central venous circulation reflecting increased right atrial pressure and dilatation of the ductus venosus. Although the above sequence of circulatory changes is typical in the growth-restricted fetus several other patterns have also been noted, such as progression to Doppler changes in the ductus venosus occurring without cerebral vasodilation developing (Baschat 2005). Others have pointed to the importance of Doppler changes at the aortic isthmus when resistance increases in the placenta (and descending aorta) but decreases in the cerebral circulation (and the aortic arch) (Fouron et al. 2009; Fouron et al. 1999).

Recent studies have provided further insight into the complexity of the cerebrovascular response to hypoxia in progressive FGR. These studies suggest cerebrovascular responses are regionally heterogeneous and that monitoring the MCA alone may not be reliable. Other studies suggest anterior cerebral artery (ACA) Doppler may be a more sensitive biomarker than the MCA Doppler changes with decreases in ACA resistance preceding those in the MCA. Given that abnormal patterns in the ductus venosus herald imminent fetal demise more direct and sensitive markers of myocardial impairment are being pursued (Benevides-Serralde et al. 2011). Power Doppler studies in FGR (Bartha 2009) have shown an early increase in frontal lobe perfusion, followed by a pronounced decrease which coincides with an increased perfusion to the deep grey matter structures (Hernandez-Andrade 2008). In the pre-terminal phase shortly before fetal demise MCA resistance may ‘normalise’ even though placental resistance remains high (Man 1991; Rizzo 1994; Weiner 1994; Mari and Deter 1992; Dubiel 2002): this paradoxical pseudo-normalisation occurs because of cardiac failure and decreased cardiac output, coinciding with central venous abnormalities. In some studies this ACA resistance remains decreased even after MCA-PI normalises, suggesting frontal lobe ‘sparing’ persists longest (Dubiel 2002).

Although a major factor in the consequences of FGR, placenta-based hypoxemia is one of many disturbances occurring in this progressive multisystem disorder. Significant impairment of placental amino acid transport develops even in the absence of significant hypoxemia, acidemia or Doppler changes. Glucose metabolism is disturbed and since gluconeogenesis is not an adaptive mechanism in FGR the fetus attempts to meet glucose requirements by increasing glucose
transport. However despite this the growth-restricted fetus has reduced circulating glucose despite normal maternal levels, a difference that increases as FGR progresses. Placental failure also decreases the enzyme 11β-HSD-2, which normally inactivates noxious cortisol to inactive cortisone levels in the fetus. The hypoxemia associated with FGR increases erythropoietin release, thereby increasing the circulating red cell mass.

**Management:** Preterm FGR is a progressive disease for which there is currently no effective intervention besides delivery, often at the risk of preterm birth. The critical challenge in preterm FGR is the safe prolongation of pregnancy, the risks of prematurity being balanced against the risk of fetal demise when delivery is delayed. Term FGR presents in the third trimester and has subtler signs of deterioration with minimal or absent Doppler features. Here the major challenge is timely detection of FGR since failure to recognise term FGR may account for over 50% of unexplained still-births near term (Froen 2004). The optimal technique for detection of imminent demise (fetal heart rate, biophysical profile or Doppler) remains controversial.

**Prognosis:** FGR fetuses have an 8-fold higher perinatal mortality than appropriately grown fetuses. In addition a broad spectrum of neurodevelopmental sequelae may occur, from cerebral destructive injury to structural and functional developmental disruption, as well as adverse fetal programming that manifests with neuropsychiatric conditions later in life. Those neurological complications presenting early in fetal and neonatal life usually have abnormal brain imaging while those with later-onset presentation such as autism, attentional disturbances, learning differences and schizophrenia (Geddes 1999) usually have normal conventional brain imaging. More advanced quantitative MRI studies have provided in vivo evidence that FGR is associated with impaired brain development in the fetus, including reduced cerebral cortical volume (Tolsa 2004), reduced hippocampal volume (Lodygensky et al. 2008) and delayed white matter maturation (Huppi 2004) which may underlie the high rate of cognitive and memory dysfunction in these fetuses magnetic resonance spectroscopy (MRS) and diffusion weighted imaging studies have shown important microstructural and metabolic differences from control AGA fetuses (Sanz-Cortes et al. 2010). Neonatal complications in FGR infants born closer to term include an increased risk of perinatal asphyxia, neonatal encephalopathy and seizures. However, neonatal outcomes are still primarily determined by effect of preterm birth, with the impact of preterm birth overriding that of deteriorating fetal status until the late second trimester (Thorton et al. 2004).

**Twin pregnancies and fetal brain injury**


Monochorionic twin pregnancies are at significant risk of fetal complications including selective fetal growth restriction, twin-twin transfusion syndrome and twin anemia polycythaemia sequence, all of which are associated with neurological sequelae in survivors. Factors that determine the risk for and type of complication in each individual include unequal placental sharing and unbalanced vascular anastomotic blood flow. Vascular anastomoses are almost universally present between the two fetal circulations and may be arterio-arterial (A-AV), arterio-venous (A-VA) or veno-venous (V-VA). Their number, size and flow direction varies significantly between monochorionic placentas. The direction of blood flow across these anastomoses can change, as resistances and pressures in the two circulations alter, with the anastomoses usually acting to balance out perfusion between monochorionic twins. Arteriovenous anastomoses are deep and unidirectional with a single cotyledon perfused by an artery of one twin and drained by a vein of the other twin. Both A-AA and V-VA are superficial and can direct blood in either direction, playing an important compensatory role when there are imbalances in volume or pressure in one fetus. The risk of fetal brain injury increases significantly if there is co-twin demise, but can occur even if both twins survive (Szymonowicz et al. 1986; Enbom 1985; Saunders et al. 1992; Bejar et al. 1991; Grafe 1993). Brain injury in the surviving twin is mediated primarily by the acute blood volume overload when the co-twin dies: necrotic thromboembolism or disseminated intravascular coagulation triggered by tissue thromboplastin from the dead twin may exacerbate injury.

**Selective Fetal Growth Restriction** (sFGR) in monochorionic twins develops in 11–14% of such pregnancies. The diagnosis of sFGR is made when the smaller twin is below the 10th centile for expected gestational age (Valsky et al. 2010). The primary determinant of fetal growth in sFGR is the proportion of placental exchange surface available to each fetus and the efficacy with which shared collateral vessels act to compensate
Table 1.7 Brain effects in Twin-Twin Transfusion Syndrome (TTTS)

<table>
<thead>
<tr>
<th>Effect</th>
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<tr>
<td>Transfusion from one twin (donor) to another (recipient) can occur in monochorionic twin pregnancies when an imbalance develops between superficial and deep anastomoses.</td>
</tr>
<tr>
<td>Brain ischaemia can occur in the donor and circulatory overload and haemorrhage in the recipient.</td>
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<tr>
<td>Brain lesions are more common in the recipient than the donor twin and include:</td>
</tr>
<tr>
<td>Hydranencephaly</td>
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<tr>
<td>Porencephaly</td>
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<tr>
<td>Polymicrogyria or mild cortical thinning</td>
</tr>
<tr>
<td>Bilateral or unilateral ventriculomegaly</td>
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<tr>
<td>Germinal matrix haemorrhage</td>
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<tr>
<td>Periventricular leukomalacia (PVL)</td>
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<tr>
<td>Reduction in volume of cerebral cortex or cerebellum</td>
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<tr>
<td>Cerebellar malformation including Dandy-Walker malformation</td>
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</table>

for any discrepancy. Multiple collaterals and larger intertwin blood flow exchange tend to lead to better outcomes than those with few connections. The placental arterial anastomoses of such individuals are large and even a brief transient period of haemodynamic imbalance such as bradycardia or hypotension in the smaller twin may cause it to experience lethal volume overload, with hypovolemia and cerebral hypoperfusion in the larger twin. Compared to other forms of mono- or dichorionic twin pregnancy the incidence of fetal demise (20%) and cerebral white matter injury is significantly higher in sFGR twins. After demise of a smaller twin mortality of the larger twin increases to 25–30% while up to 30% of survivors sustain brain injury (Valsky et al. 2010). To date the best biomarker for management and prognosis in monochorionic twin pregnancies with sFGR is the uterine artery Doppler pattern in the sFGR twin where different patterns have been described and are reviewed in detail elsewhere (Gratacos et al. 2004b). The development of absent or reversed diastolic flow (AREDV) in the umbilical artery of the smaller twin, which occurs in 40% of sFGR patients, is an important risk factor for fetal demise and brain injury (Gratacos et al. 2004b). Importantly, this brain injury occurs significantly more in the larger twin even if the smaller twin survives: in fact, the incidence of brain injury in normally grown co-twins of sFGR twins with AREDV approaches 40% (Gratacos et al. 2004b). Other risk factors for brain injury in monochorionic twins with sFGR are the need for preterm delivery for many patients as well as the high risk of acute fetofetal transfusions with brain injury in the larger twin (Gratacos et al. 2004a, 2007; Ishii et al. 2009).

Twin-twin transfusion syndrome (TTTS) complicates approximately 10–15% of all monochorionic twin pregnancies. Untreated TTTS has a perinatal mortality of over 80% (Lewi et al. 2008a, b; Denbow et al. 1998) with a 15–20% risk of neurological injury in survivors (Lopriore et al. 2007; Crombleholme 2012). Factors predisposing to this complication include evidence of circulatory disequilibrium between the twins and unidirectional flow in deep A-VA not countered by sufficient superficial A-AA (Denbow et al. 2000; Taylor et al. 2000). Superficial A-AA on the chorionic plate surface are a good biomarker for the development and severity of TTTS; absence of such A-AA confers a 78% risk of TTTS (Denbow et al. 2000). With loss of circulatory equilibrium the recipient twin develops hypervolemia, polyuria and polyhydramnios while the opposite features develop in the donor twin. The TTTS has a multisystem impact in the fetus, especially on the heart and kidneys: volume overload in the recipient leads to polyuria and polyhydramnios as well as myocardial hypertrophy, depressed myocardial function, abnormal venous Doppler measures and tricuspid regurgitation (TTTS cardiomyopathy), with fetal hydrops and demise ultimately occurring. The donor twin develops renal atrophy, a small heart and bladder, oliguria and oligohydramnios, which if especially severe can lead to a ‘stuck twin’ situation with amniotic membranes wrapped around the growth-restricted fetus.

Management of TTTS is guided by multilevel staging schemes of severity (Quintero et al. 1999; Villa et al. 2014). Current treatment options include conservative management through amnioreduction (percutaneous needle removal of amniotic fluid) to reduce polyhydramnios and the risk of preterm labour. More invasive approaches include fetoscopic laser surgery aimed at occluding anastomoses to improve circulatory balance or selective fetocide by cord occlusion, usually of the recipient fetus. Review of previous studies show that after amnioreduction overall mortality ranges from 43% to 77% (Rossi and D’Addario 2008; Mari et al. 2001; Gray et al. 2006; Li et al. 2011a) with major neurodevelopmental impairment in 14–26% of survivors (Lopriore et al. 2003; Frusca et al. 2003). In a recent report survivors of TTTS treated with amnioreduction had neurodevelopmental impairment in 30% while cranial ultrasound abnormalities were present in over 50% (Li et al. 2011a). Conversely, mortality after fetoscopic laser surgery ranges from 38% to 81% (Rossi and D’Addario 2008), however, more recent advances in laser surgery in TTTS have been associated
with improving survival and neurological outcome: in the largest reported study major neurodevelopmental impairment was seen in 18% of survivors at 2 years of age (Lopriore et al. 2009). Overall, the risk of adverse neurological outcome in TTTS is high regardless of treatment: this is related to the fetal haemodynamic and haematological imbalances (Havercamp et al. 2001) and the risks of preterm birth (Lutfi et al. 2004) as well as low birthweight (Frusca et al. 2003). In fact, the outcome for TTTS appears vastly improved when both fetuses are born alive after 27 weeks (Mari et al. 2000, 2001). Therefore, the central goal for management of TTTS should be prolongation of pregnancy (Li et al. 2011a).

**Twin Anaemia Polycythaemia Sequence (TAPS)** results when slow twin-twin blood transfusions occur through very small placental anastomoses in monochorionic twin pregnancies, either spontaneously or after laser therapy for TTTS. TAPS is characterised by large haemoglobin differences but no significant amniotic fluid differences. Severe brain injury and fetal demise may develop as a consequence of polycythaemia and hyperviscosity (Lopriore et al. 2013). In monochorionic twin pregnancies widely divergent peak systolic velocities on middle cerebral artery Doppler should suggest the diagnosis of TAPS, velocities being high in the anemic donor and low in the polycythemic recipient.

**Fetal Brain Insults of Fetal Origin**

Fetomaternal haemorrhage with transfer of small amounts of fetal blood to the maternal circulation is likely to occur in most pregnancies. The neurological consequences for the fetus depend on the acuity and volumes of blood transferred. Fetomaternal haemorrhage results from disruption of the placental trophoblast and in most patients the aetiology remains unknown: a decrease or loss of fetal movements is the most common presentation (Giaconia 1997). Small amounts of transfusion are invoked in conditions such as alloimmunisation in Rh (–) mothers (with haemolysis, anaemia and jaundice in the fetus) and alloimmune thrombocytopenia. Large transfusions, especially when acute, may result in fetal hypovolemia, neurological injury and fetal demise (Wylie 2010). Chronic fetomaternal haemorrhage may result in fetal anaemia and decreased oxygen carrying capacity with subsequent end-organ injury; especially in the context of sudden superimposed stressors such as complicated labour. Chronic low-grade fetomaternal haemorrhage may lead to fetal anaemia with a characteristic increase in the peak systolic Doppler velocity in the middle cerebral artery. The standard Kleihauer-Betke test has limitations but remains the first line diagnostic test: treatment of fetal anaemia is complex and may require repeated percutaneous fetal blood transfusions.

**Brain injury secondary to fetal malformations.** Certain fetal malformations may lead to secondary fetal brain injury or developmental anomalies, especially conditions that cause disturbances in the fetal circulation and oxygenation. Certain cardiac malformations, most notably transposition of the great arteries and hypoplastic left heart syndrome, may be associated with hypoxemia and/or hypoperfusion of the fetal brain. Fetal imaging with Doppler and MRI studies have shown decreased cerebral vascular resistance (presumably compensatory) (Donofrio et al. 2003; Limperopoulos et al. 2010) as well as cerebral lactate (suggestive of anaerobic metabolism) (Limperopoulos et al. 2010) in these conditions. Over the course of the third trimester there is delay in sulcal gyral development (Clouchoux et al. 2012a) and a fall-off in volumetric brain growth (Limperopoulos et al. 2010) in these fetuses. Large congenital diaphragmatic hernias may interfere with left ventricular function and impede cerebral venous drainage, thereby exposing the fetal brain to risk of hypoperfusion-hypoxia.

Progressive fetal hydrocephalus is a risk factor for acquired periventricular parenchymal injury due to either mechanical stress on axons or impaired regional perfusion (Del Bigio et al. 1994; Guzzetta et al. 1995). In addition, certain vascular lesions may cause high output cardiac failure in the fetus with secondary effects on fetal cerebral perfusion: examples of such lesions are large, vascular sacrococcygeal teratomas and vein of Galen malformations.

**The Intrapartum Period**

**Tolerance of Labour:** Impaired exchange of critical substrates between the maternal and fetal circulations may occur during labour. The contractile forces of normal labour may interrupt, usually briefly, both utero-placental and fetal placental circulations. Myometrial contractions compress uterine artery branches especially the spiral arteries, decreasing perfusion to the intervillous spaces, while increased intrauterine pressure may compress the umbilical vein and artery, especially after membranes are ruptured. By definition these decreases in perfusion impair materno-fetal gas exchange making labour an intrinsically asphyxiating process. The impact on the fetal brain from these systemic asphyxiating insults depends to a large extent on the integrity of compensatory mechanisms aimed at maintaining preferential cerebral supply of oxygen and nutrients (see above).

That the vast majority of fetuses survive the insults of labour apparently unscathed is due in large part to the adaptive haemodynamic responses activated during the transient fetal hypoxia associated with uterine contractions. The ability of the fetus to withstand the rigors of labour depends on both the integrity of these compensatory fetal responses as well as the nature of the asphyxial insult. In a small percentage of patients these adaptive fetal mechanisms are overwhelmed because of preceding placental and/or fetal compromise or dysfunctional labour or both (Low 1997). With collapse of these protective responses the fetus becomes exposed to brain insults and potential brain injury: the consequences of such insults range from transient neonatal encephalopathy to lifelong neurological complications (Volpe 2001) the most prevalent of which are CP epilepsy and cognitive impairment.

The importance of identifying the fetus likely to be intolerant of labour, or to identify when such intolerance develops...
Part I  Fetal and Neonatal Neurology

during labour, relates to the importance of timely responses to prevent or limit brain injury as a consequence. A multitude of agents have shown neuroprotective efficacy in experimental models where the insult is timed and interventions can occur before, during or very soon after such insults; however, the vast majority of these agents have failed in human clinical trials. One important reason for this is our current inability to anticipate or detect brain insults within the therapeutic window of these neuroprotective agents.

The initial events during the development of intrapartum asphyxia are fetal hypoxemia and hypercarbia. These phenomena are normally transient, waxing and waning with contractions; however, if contractions are sustained, frequently repeated without ‘recovery’ or compensatory mechanisms compromised hypoxemia will lead to metabolic acidosis. Intrauterine asphyxia may be considered pathological when impaired materno-fetal gas exchange circulations leads to anaerobic cellular metabolism and the accumulation of lactate, ‘significant’ metabolic acidosis, causing eventual energy failure in the fetus. Although the criteria for diagnosing significant metabolic acidosis in fetal asphyxia remain an open debate the commonly used clinical threshold is an umbilical artery pH of 7.00 or below, with a base deficit above 12mmol/L (Low et al. 1997; Gilstad et al. 1989; Goldaber et al. 1991; American College of Obstetricians and Gynecologists 2014). Although fetal asphyxia as defined by these clinical criteria complicates around 2% of births (Low 1997; Low et al. 1997) the insult is usually mild and the fetal impact minimal (Low 1997; Low et al. 1997). For reasons discussed below these diagnostic criteria for asphyxia are in isolation, at best, weak prognostic indicators of long-term neurological outcome (Ruth and Raivio 1988; Fee et al. 1990). In only about 0.4% of infants is the asphyxial insult severe enough to cause at least transient organ (including brain) dysfunction (Low 1997; Low et al. 1997) with only 0.1% of live births associated with asphyxial brain injury and irreversible neurological sequelae (Low et al. 2001).

Neither fetal asphyxia nor the ensuing brain in term infants the severity of neonatal encephalopathy after asphyxia is often predictive of later neurological disability, as described in the 2014 report of the American College of obstetricians and Gynecologists. Injury is mediated by a single mechanism: instead, the potential pathways leading to these pathological states are multiple (du Plessis and Johnston 1997; Johnston et al. 2001). What follows is a conceptual overview of the factors involved in the asphyxial insult, the adaptive responses of the fetus to preserve cerebral oxygenation and the consequences of eventual failure of these compensatory mechanisms.

Broadly speaking, fetal tissue hypoxia may result from reduced circulating arterial oxygen content (i.e. hypoxic-hypoxia or anemic-hypoxia) or inadequate tissue perfusion (ischaemic-hypoxia). These mechanisms may originate in the mother, the uteroplacental unit, the fetoplacental unit or the fetus itself. Maternal causes of fetal asphyxia include maternal hypotension or cardiac arrest, maternal pre-eclampsia or myometrial hypercontractility during labour. All these conditions cause a decrease in uterine perfusion, leading to ischaemic hypoxia in the placental intervillous spaces and ultimately hypoxic-hypoxia in the fetus (Brinkman et al. 1974). Placental causes of fetal asphyxia include placental abruption, placenta previa, vasa previa or feto-maternal haemorrhage, all of which may cause fetal hypovolemic cardiac failure and rapid ischaemic-hypoxia. Other causes, such as twin-to-twin transfusion in monochorionic twins, may result in more gradual fetal anemic hypoxia. Occlusion of a malpositioned umbilical cord may cause relatively brief but repeated insults during uterine contractions; conversely, nuchal entwining of the cord may cause prolonged, variable compression, while cord prolapse may cause severe and sustained compression. Fetal causes include anemia (e.g. Rh-incompatibility, parvovirus infection) leading to anemic-hypoxia or certain congenital malformations such as congenital heart disease, in which circulatory disturbances may result in cerebral hypoperfusion or hypoxemia.

Cellular Mechanisms of Intrapartum Hypoxic–Ischaemic Cerebral Injury

The overall oxygen demand of the immature brain is significantly lower than that of the mature brain (Altman et al. 1988; Altman et al. 1993). However, although the global cerebral oxygen demand is low regions of most active maturation at a particular gestational age have particularly high oxygen demands, necessary to support the activity of enzymes critical for neuronal development, such as those involved in ion homeostasis (e.g. Na K-ATPase) (Mihara et al. 1988) and oxidative metabolism (Chugani et al. 1987; Clark 1994). These regions of elevated oxygen metabolism are particularly vulnerable to hypoxia: during fetal asphyxia failure to satisfy these regional energy demands leads to the rapid depletion of available energy substrate and unleashes cellular processes of injury and the cell death cascade.

The excitatory neurotransmitter glutamate plays an essential role in normal brain development (Johnston et al. 2001; McDonald and Johnson 1990). Through action at specific receptors on the neuronal membrane glutamate is critical for maturational processes such as neuronal differentiation dendritic arborisation, synapse formation and plasticity. Normal activation of these glutamate receptors, particularly the N-methyl-D-aspartate (NMDA) receptors, triggers the highly regulated passage of calcium through the receptor ionophores, thereby providing critical trophic support for neuronal development. The normal control of calcium conductance through the ionophores of these NMDA receptors is dependent upon regulation of the neuronal membrane potential by energy-dependent ion pumps. In regions of particularly active neuronal development the glutamate system is ‘primed’ in several ways to facilitate the cytosolic calcium influx including a regional increase in glutamate receptor density and the enhanced calcium conductivity of these immature receptors.

When cerebral energy failure develops in fetal asphyxia the tight regulation of this glutamate system is lost, causing massive pre-synaptic glutamate release and decreased
glutamate reuptake: this results in toxic levels of glutamate accumulating in the synaptic cleft (Johnston et al. 1992; Riikonen et al. 1992). The combination of sustained glutamate receptor activation and neuronal membrane depolarisation maintains glutamate calcium channels open to a massive, uncontrolled influx of calcium into the neuronal cytosol where potentially lethal processes of cellular injury are activated. The dichotomous roles of glutamate in normal brain development and in 'excitotoxic' injury during hypoxia-ischaemia help to explain the distribution of brain injury in fetal asphyxia. Glucose metabolism plays a complex role in hypoxic-ischaemic brain injury. During the early phases of asphyxia failure of oxidative metabolism with a persistence of cerebral glucose supply activates glycolysis and lactate production. The accumulation of lactate during cerebral hypoxia-ischaemia has a biphasic effect on the immature brain: in animal models lactate accumulation has an initial beneficial effect in part because of its role as an alternative fuel source in the immature brain (Vannucci, Bruchlaker, et al. 1996) however in studies with sustained high levels of lactic acidosis, deleterious processes are initiated whether the levels of cerebral lactate developing during asphyxia remains controversial. Glucose is critical for the reuptake by astroglial cells of glutamate from the extracellular space. (Magistretti 1999) thus, hypoglycemia may trigger or exacerbate excitotoxic brain injury. During periods of prolonged asphyxia exhaustion of fetal hepatic glycogen stores may result in hypoglycemia: the resulting combination of energy failure (due to hypoxia and hypoglycemia) and accumulation of extracellular glutamate may lead to profound cerebral injury.

**Topographic Patterns of Brain Injury During Fetal Asphyxia:** Although the critical insult during fetal asphyxia, i.e. cerebral hypoperfusion, is typically generalised the topography of the resulting brain injury tends to be focal or regional. The regional distribution of brain injury is determined by many factors including gestational age (i.e. level of cerebral and vascular development) and the nature (intensity and duration) of the insult. The relationship between gestational age and the topography of brain injury is determined in large part by the regional differences in brain maturation (and thus regional differences in metabolism) at the time of insult. The specific regions of brain injury in turn determine the clinical picture of subsequent neurological deficits in survivors and although the relationship between insult, injury, and outcome remains only partially understood techniques such as brain MRI have provided important insights (discussed below).

At a tissue level two broad types of hypoxic–ischaemic brain injury can be distinguished in the asphyxiated newborn–infant, i.e. selective cellular injury and pancellular necrosis (infarction). In each infant the type of injury and the distribution of such are determined by factors such as the gestational age and the intensity, duration and number of insults. Although any cell type may be injured by hypoxia-ischaemia certain cell types are selectively vulnerable at different gestational ages. In the preterm fetus the immature premyelinating oligodendrocyte (Back et al. 2001) is particularly vulnerable to selective cellular injury while at term gestation selective cellular injury tends to be mainly neuronal although in regions of active myelination the mature oligodendrocyte is also vulnerable. The regional distribution of selective cellular injury (neuronal and oligodendrocyte) may be categorised into several broad patterns. At term, the most actively maturing (and therefore most vulnerable) neurons are in the basal ganglia and thalamus, brainstem nuclei, hippocampus and regions of the neocortex, especially the peri-rolandic and visual cortices (Maller et al. 1998). Within the cortex neuronal injury is most severe in the deeper layers particularly in the depths of the sulci as discussed above, the vulnerability of these areas of intense regional maturation (Piggott 1993) relates to their high glutamate–receptor density and reactivity as well as the high metabolic demands of neuronal maturation and axon myelination.

The regional distribution of cerebral infarction that occurs during global cerebral hypoperfusion is also determined by the maturational state of the cerebral vasculature. These regions of infarction tend to develop in the watershed territories between the cerebral arterial end-zones. In the term infant the major watershed regions are in the end-zones between the anterior, middle and posterior cerebral artery territories of supply; consequently infarction develops in the parasagittal regions along the superolateral convexity of the cerebral hemispheres.

Perinatal asphyxia may also be complicated by vaso-occlusive insults and infarction in the territories of arterial supply or venous drainage (see Chapter 2). Arterial occlusion or stroke is more common in the term infant and usually involves the middle cerebral arteries, particularly the left. Venous occlusion usually occurs in the dural veins most commonly in the posterior part of the superior sagittal sinus and less commonly in the surface cortical veins or deep venous system. Although any type of infarction is susceptible to haemorrhagic transformation this is more typical of venous infarction: these vaso-occlusive injuries are discussed in detail elsewhere.

The other major determinant of the topography of brain injury in fetal asphyxia is the insult ‘dose’ which is in turn determined by the intensity and duration of the insult. The intensity of asphyxial insults may be divided broadly into partial or severe insults: prolonged partial insults at term tend to concentrate injury in the parasagittal watershed areas of cortex and subcortical white matter with relative sparing of the deep grey regions. This pattern of parasagittal cerebral injury has been well described in a term primate model of prolonged partial asphyxia.

With severe asphyxia the regional distribution of injury is determined by the duration of insult. Regardless of gestational age infants surviving prolonged and severe circulatory collapse (e.g. 20–30 minutes or more) develop diffuse rather than regional cerebral injury, with devastating neurological sequelae. Conversely, with severe insults of brief duration gestational age does influence the distribution of cerebral injury. At term such brief but severe insults tend to concentrate neuronal injury.
in the basal ganglia, thalamus, hippocampus, sensorimotor cortex and white matter injury in the corticospinal tracts from the sensorimotor cortex to the internal capsule, as well as the optic radiations. Interestingly, in fetal sheep basal ganglia injury may also follow repeated brief insults while prolonged partial insults cause hippocampal injury. These neuropathologic patterns of injury were initially described at autopsy but can now be detected by neuroimaging studies, especially MRI.

FETAL NEURODIAGNOSTIC TECHNIQUES

Prenatal Screening Tests
As part of prenatal screening programmes maternal serum AFP performed between 16 and 18 weeks of gestation is used to screen for neural tube defects, from anencephaly to spina bifida. However, maternal serum alpha-fetoprotein may be falsely elevated in twin pregnancies, abdominal wall defects (omphalocele, gastroschisis) and duodenal atresia, as well as falsely decreased in insulin-dependent diabetes and maternal obesity. Amniotic fluid measures of AFP are highly sensitive for anencephaly and open neural tube defects and can be further enhanced by measures of acetylcholinesterase which is primarily neuronal in origin.

Prenatal Genetic Testing
Cyto genetic studies on fetal (amniocentesis) or chorionic villous sampling cells have been in practice for many years; however, advances in understanding of the genome and newer technologies have significantly increased the utility of this approach for establishing or confirming a specific genetic diagnosis. Indications for cytogenetic testing are several and the specific test may be determined by the phenotypic features on fetal imaging or the level of risk based on the maternal and family history. The earliest and still the most common indication for chromosomal studies is to exclude Down syndrome while the sampling of genetic material for cytogenetic studies may be achieved through amniocentesis, CVS and more recently cell-free fetal DNA from maternal blood. Full karyotype analysis remains the most common cytogenetic technique; however, karyotyping has limitations including long turnaround time, labour intensity and cost: the delayed diagnosis of 1 to 2 weeks is an issue if decisions about continuation of pregnancy need to be made urgently. Fluorescent in situ hybridisation (FISH) has a much faster turnaround (24–48 hours) and provides a provisional chromosome ‘count’ however definitive testing still requires formal karyotyping. The FISH technique can also be performed when specific chromosomal microdeletions are suspected on the basis of family history or phenotype. Microarray analysis is an extension of the FISH technique that allows more detailed examination of specific regions of the genome. The field of neurogenetics, in particular, has benefited enormously over the last decade from the large body of integrated genomic data linking brain malformations to specific gene loci: the advance in microarray-based testing, such as microarray-comparative genomic hybridisation, applied to the genome-wide study of specific neurogenetic disorders, have identified the submicroscopic chromosomal loci for many of these conditions. In addition, different genetic mutations may be associated with a specific malformation category but allow subtyping and more refined prediction of outcome: examples include the holoprosencephaly, lissencephaly and callosal agenesis spectra, all of which are discussed in more detail above.

Maternal fetal trafficking and non-invasive fetal testing: Despite the commonly held belief that the maternal and fetal circulations are separate bidirectional cell trafficking occurs and fetal cells can be found in the maternal tissues and vice versa. Earlier the focus was on extracting DNA from nucleated fetal red blood cells but the number of intact fetal cells is markedly less than maternal cells, impeding this approach. The more recent focus on cell-free fetal DNA (cffDNA) in the circulation of the mother has created and exciting new non-invasive approach to fetal testing.

Circulating cell free DNA in the maternal serum contains both maternal and fetal components, with the fetal fraction increasing to as high as 50% with normal gestation (Ferres et al. 2014; Fan et al. 2012) and increasing further in conditions such as pre-eclampsia: cffDNA can also be amplified using polymerase chain reaction (PCR). Such cffDNA is now thought to arise primarily from placental trophoblastic cells and less so from fetal haematopoietic cells. This non-invasive prenatal testing approach has already entered the clinical arena although it is currently confined to testing for aneuploidy, (especially the trisomies) and sex in patients where sex-linked genetic syndromes are suspected (Ferres et al. 2014). Although cffDNA testing is not diagnostic for the aneuploides the very high specificity has already reduced the number of invasive procedures like amniocentesis or chorionic villus sampling, which are not without risk. This approach has exciting potential for more expanded testing in future, such as the study of fetal mRNA of placental origin in the maternal circulation (Poon et al. 2000; Ng et al. 2003) and testing for duplications and microdeletions in conditions such as Prader-Willi/Angelman syndrome (15q11–q13), Miller-Dieker syndrome (17p13.3) and Di George syndrome (22q11.2). When specific chromosomal regions are of interest more focused or targeted sequencing allows more rapid and less costly analysis. Epigenetic changes describe the environmental effects on gene function, without changing the DNA sequence: these changes are heritable and affect gene expression by turning genes on or off. Of great interest is the potential to detect epigenetic markers, including DNA methylation, histone modifications and genomic imprinting, on the fragments of cffDNA. Fetal microRNA (miRNA) can also be detected in the maternal serum; miRNA are small non-coding RNA molecules which function in RNA silencing and
post-transcriptional regulation of gene expression. A specific group of miRNAs called epi-miRNA can directly target the effectors of epigenetic mechanisms and alter gene expression. This approach holds great promise for the future ability to detect the impact of environmentally mediated phenotypic plasticity of not only the fetus but also the placenta as a result of influences such as stress, toxins, inflammation or conditions such as maternal diabetes or pre-eclampsia. Preliminary studies have suggested that hypoxia-induced fetal RNA transcripts in the maternal circulation can be quantified and that these correlate with fetal hypoxic status (Whitehead et al. 2013).

**FETAL NEUROIMAGING**

**Fetal Ultrasound Imaging**

Antenatal ultrasound revolutionised the field of fetal medicine over four decades ago. This prolonged experience with fetal ultrasound has provided a well-established body of normative biometric data, including measures of head circumference, biparietal diameter and ventricular size. Despite the more recent advent of MRI, fetal ultrasound remains the first-line screening modality choice for the fetal brain. Fetal ultrasound has undergone major advances in both image quality and application: imaging quality has improved significantly with development of high-frequency, three-dimensional transducers. Transvaginal fetal ultrasound has overcome some of the limitations of transabdominal ultrasound (see below). Fetal Doppler ultrasound has enabled evaluation of the fetal circulation including fetal cerebral haemodynamics, such as the autoregulatory ‘brain-sparing’ response to hypoxemia in fetal growth restriction and certain fetal heart lesions (Baschat et al. 2001; Donofrio et al. 2003). Three-dimensional ultrasound has many potential applications including volumetric measurements; however it is primarily used for determining the extent of craniofacial and skeletal disorders (Merz et al. 2012; Merz and Abramowicz, 2012; Chen et al. 2005; Cassart et al. 2007) as well as providing surface rendering of the fetus. Four-dimensional ultrasound is not widely used but has opened windows of opportunity for the real-time assessment of fetal movements and behaviour (Kurjak et al. 2012; Sato et al. 2014).

Standard screening protocols for the timing and level of fetal ultrasound vary regionally. First trimester fetal ultrasound is used to confirm the presence of a beating-heart fetus and establish gestational age. In addition first trimester ultrasound indices (e.g. the nuchal translucency) are part of a panel of routine screening measures which together with maternal biochemistry screening serve to identify risk for aneuploidies and major anomalies. In certain centres first trimester is being used to provide earlier diagnosis of specific conditions such as congenital heart disease (Persico et al. 2011; Johnson and Simpson 2007). Later, usually between 18 and 22 weeks when most major anomalies can be detected, a more detailed anatomic survey is performed: a normal first trimester ultrasound should not replace this 18–22 week anatomy scan. Ultrasound also forms part of integrated fetal testing panels such as the biophysical profile, used for monitoring high-risk pregnancies.

Antenatal testing by ultrasound includes Doppler measurements of blood flow impedance in the different tissue types. Doppler ultrasound is an important tool for following the progression of diseases such as fetal growth restriction and polyhydramnios. Both fetal ultrasound and Doppler are used in high-risk patients as part of the biophysical profile and non-stress testing.

**Fetal Brain MRI**

Because of superior soft tissue resolution MRI has become the principal tool for visualising brain structure. Adaptation of MRI to the fetal brain has played a major role in the advance of fetal neurology as a discipline: fetal MRI offers three-dimensional resolution, multiplanar imaging capabilities, large field of view and robust image quality. Overcoming the obvious challenges of imaging the fetus, particularly spontaneous fetal movements and maternal breathing, required development of ultrafast sequences that minimise motion artifact. The development of ultrafast T2-weighted sequences and improved MRI hardware enabled acquisition of single T2-weighted slices in less than one second, eliminating the need for sedation (Huisman et al. 2002; Glenn 2009). These sequences provide superb contrast between tissue and cerebrospinal fluid, especially useful for assessing cortical development (Levine 1996). T1-weighted inversion recovery and proton density sequences can be used to detect hyper-intense lesions such as haemorrhage, lipoma, subependymal nodules or calcifications and myelination patterns (Girard et al. 2006a; Glenn 2009); however, T1-weighted images of the fetal brain are more difficult, especially before the end of the second trimester, primarily because of their longer acquisition times which makes them prone to motion artifact. This limitation reduces the ability to detect haemorrhage and calcification by fetal MRI. More recently, T2* sequences have been used to detect blood-breakdown products. Susceptibility-weighted MRI is sensitive to blood, blood products and calcification and, therefore, might provide important information about acquired disruptive aetiology. Diffusion weighted imaging using single-shot, echo-planar diffusion imaging can be acquired in less than 15–20 seconds and assist in identifying destructive brain lesions. Diffusion weighted imaging is used to identify focal areas of reduced or increased diffusion following acute ischaemic injury (Righini et al. 2003; Schneider et al. 2007; Schneider et al. 2009): in addition, fetal DWI has been used to identify delayed brain development and decreased microstructural organisation in high-risk groups such as small-for-gestational-age fetuses (Sanz-Cortes et al. 2010). Diffusion tensor imaging (DTI) assesses white matter microstructural architecture (Basser et al. 1994) by evaluating axonal/fibre formation and connectivity in the developing
myelination. In addition, \( ^1H \)-MRS can identify a lactate peak suggestive of anaerobic metabolism (Girard et al. 2006b; Limperopoulos and Clouchoux 2009), although this is debated.

As the principal diagnostic modality for detecting parenchymal brain lesions (both dysgenetic and acquired) in the fetus MRI plays a critical role in fetal counselling. In countries where pregnancy termination is legal the outer gestational age for these procedures is often around 22–24 weeks gestation. However many critical processes of brain and especially cortical development are far from complete at this stage, leaving uncertainty about suspected but subtle cortical anomalies. When fetal brain status is likely to impact on important intervention decisions immediately after birth the status of third trimester cortical development can be assessed by a follow-up third trimester MRI study.

Advanced Quantitative MRI techniques have become well-established tools for the study of the postnatal brain. Despite significant challenges of bringing some of these techniques into the fetal arena, a number of centres have successfully applied quantitative MRI to the fetal brain. As opposed to the current clinical standard for fetal MRI, based largely on a subjective pattern-recognition approach, these quantitative techniques have the potential for significantly greater sensitivity to brain changes and in particular detecting the earliest deviations of brain growth trajectories. In so doing these techniques will advance our understanding of the timing and progression of insults that disrupt normal brain development.

Three-dimensional volumetric MRI has been enabled by combined motion correction algorithms and 3-D reconstruction techniques developed specifically for fetal MRI (Rousseau et al. 2006; Jiang et al. 2007; Kim et al. 2010): this approach allows measurement of global and regional brain growth and provides previously unavailable in vivo fetal brain growth curves (Habas et al. 2010; Clouchoux et al. 2011; Rajagopal et al. 2011). Similarly, studies are providing the first description of gyral development in the human fetal brain during the critical period of rapid cortical development in the second and third trimester (Clouchoux et al. 2011; Habas et al. 2011).

Fetal brain MRI versus ultrasound, strengths and weaknesses. Fetal ultrasound and MRI techniques each have unique strengths and weaknesses and should be used in a complimentary manner when evaluating the fetal brain (Levine 2001; Levine 2002; Pugash et al. 2008). Fetal ultrasound is non-invasive, relatively inexpensive, easily repeatable and allows real-time exploration of the fetus, features that make it the preferred technique for monitoring change such as the size of lesions including fetal ventriculomegaly. However, although ultrasound will remain the screening modality of choice, MRI is the diagnostic modality when abnormalities are noted by ultrasound. Echogenicity increases at the interface between fluids and membranes: for this reason ultrasound may better detect thin structures such as the walls of cystic lesions (e.g. Blake’s pouch cysts, arachnoid cysts, choroid plexus cysts) than MRI. Ultrasound is also better at identifying calcifications as well as lenticulostriate vasculopathy, seen in congenital infections such as CMV and toxoplasmosis. Fetal ultrasound identifies intraventricular haemorrhage but MRI better localises choroid plexus haemorrhages. Fetal MRI provides superior detection of blood breakdown products in and around the brain parenchyma. Fetal ultrasound reliably measures ventricular diameter and identifies ventriculomegaly: it can also identify a posthaemorrhagic aetiology for hydrocephalus but MRI better establishes aqueductal stenosis as the cause by showing narrowing of the distal aqueduct. Prior to 20 weeks MRI resolution is overall poor because of the normally enlarged ventricles, thin cerebral mantle and thick germinal matrix (Girard et al. 2009): subsequently however the superior tissue resolution of MRI better identifies parenchymal loss, diffuse white matter abnormalities and small lesions (e.g. heterotopias). Fetal MRI is particularly valuable for delineating lamination of the cerebral mantle in the second trimester and gyral-sulcal development in the third trimester cerebral cortex. Between 20 and 28 weeks gestation the cortical mantle has a multilayered appearance on MRI (Girard and Raybaud 1992; Girard et al. 1995; Chong et al. 1996; Brisse et al. 1997; Kostovic et al. 2002; Garel et al. 2003; Garel 2004; Prayer et al. 2006) which represents the ventricular, periventricular, subventricular, intermediate and subplate zones, as well as cortical plate of the developing fetal brain (Kostovic et al. 2002; Rados et al. 2006). In the third trimester the emergence of sulci and gyri follows a consistent spatial and temporal programme. MRI best detects disturbances in cortical development (e.g. lissencephalies and polymicrogyria) (Glenn et al. 2005) as well as subependymal lesions (e.g. tubers, heterotopias and cysts). Bone attenuates the ultrasound signal causing acoustic shadowing which makes MRI superior for delineating posterior fossa structures, especially the vermis and brainstem. Furthermore, calcification of the calvarium in the third trimester and maternal pelvic bones obscures visualisation of the fetal brain by ultrasound (Glenn and Barkovich 2006): although adipose tissue degrades both ultrasound and MRI signals, the former is more compromised. These limitations can be reduced by transvaginal and high-frequency ultrasound transducers: as discussed above, fetal motion has been a major challenge for the advance of fetal MRI but not
for fetal ultrasound. Abnormalities in amniotic fluid volume present different challenges to the two techniques: the increased range of fetal movements makes motion artifact particularly challenging for MRI in patients affected by polyhydramnios, until the fetal head becomes stabilised by the maternal pelvis in late gestation. Conversely, oligohydramnios limits the resolution of ultrasound but not MRI, with contraindications to MRI including ferromagnetic implanted devices and certain tattoo materials, as well as maternal claustrophobia.

**NON-INVASIVE TECHNIQUES FOR MONITORING FETAL HYPOXEMIA AND ACIDOSIS**

Direct percutaneous needle sampling of fetal cord blood was performed more commonly in the past and provided valuable insights into the development of fetal hypoxemia and acidosis in conditions such as placental-based fetal growth restriction (Nicolaides et al. 1986). In recent years an integrated panel of non-invasive tests have largely replaced cord blood sampling in the monitoring of conditions at high risk for fetal compromise. The fetus can usually tolerate moderate chronic hypoxemia for long periods of time without collapse (Longo and Pearce 1991; Pearce 2006); however, chronic fetal hypoxemia increases the risk of fetal demise, intrapartum metabolic acidosis and long-term neurodevelopmental impairment. Antepartum hypoxia reaches a critical risk threshold for catastrophic fetal decompensation and ultimately demise when fetal hypoxemia progresses to metabolic acidosis (Turan et al. 2008a, b; Manning 2009). Turan et al. 2008b; Manning 2009). 'Significant' fetal academia has been strongly associated with perinatal mortality and morbidity including neurological adverse outcomes. Early-onset FGR is associated with significant risk for preterm birth, both spontaneous or elective while preterm infants born acidotic are at significantly higher risk of adverse neurological outcome and perinatal demise (Locatelli et al. 2010; Baschat et al. 2007). The panel of diagnostic modalities used to monitor these patients for signs of decompensation combines and integrates the strengths of fetal ultrasound, heart rate and Doppler ultrasound to obtain scores, such as the biophysical profile score (BPS).

**Fetal heart rate analysis** is used for the fetal *non-stress test* and is part of BPS. The fetal heart rate is used as a downstream surrogate for brainstem and hypothalamic autonomic systems of cardiovascular control, systems that are sensitive to hypoxemia (Baser et al. 1992). In current practice the FHR is assessed by visual inspection for baseline rate, accelerations and decelerations however these are influenced by a number of other factors including the maturational and behavioural state of the fetus. The *non-stress test (NST)* links fetal movements to heart rate accelerations and is one of the most sensitive tests for fetal hypoxemia. A normal NST must show at least two accelerations within 20 minutes as well as a normal fetal heart rate and variability: absence of accelerations is considered a non-reactive NST. Elsewhere, while a reactive NST is reassuring for the absence of fetal hypoxemia a non-reactive NST has poor specificity. Studies in fetal sheep have shown a progressive loss of FHR variability with increasing fetal acidemia, reflecting a loss of normal autonomic influence on the heart rhythm. A more detailed review of the basis for FHR testing can be found elsewhere (Bennet and Gunn 2009).

The **biophysical profile (BPS)** uses a multivariable approach assigning a score between zero and two points for each of five fetal variables with a maximally reassuring score of 10 points. The five modalities assessed are breathing movements, body movements, tone/posture, heart rate and variability and amniotic fluid assessment. A score of 8 or more is associated with a very low incidence of acidemia (pH<7.25) (Manning et al. 1993). Fetal breathing movements are suppressed early in the development of hypoxemia. Fetal tone is assessed largely by posture and only valid when there are at least some fetal movements during the study: absent fetal tone correlates strongly with fetal acidosis. During a BPS study fetal movements eliciting an acceleration of heart rate are reassuring whereas lack of accelerations or decelerations associated with fetal movements is considered non-reassuring.

**Amniotic fluid volume** decreases when circulatory centralisation in the hypoxic fetus leads to redistribution of perfusion away from the kidneys; however, the relationship with acidosis is not clear.

The **fetal behavioural variables** of fetal tone, movement and breathing activity are centrally mediated and can be studied by fetal ultrasound: progressive fetal hypoxemia and acidemia have fairly predictable effects on these behaviours (Ribbert et al. 1993). Fetal breathing movements decrease first but loss of gross body movements and tone are the most consistent predictor of fetal academia and usually cease at a pH around 7.10 (Vintzileos et al. 1991). The response of fetal behaviours to progressive hypoxemia appears to be hierarchical with FHR variability disappearing first, followed by respiratory activity and then loss of fetal movements.

**Doppler ultrasound**, which measures velocity and resistance of regional blood flow, has become a powerful technique for monitoring the progression of conditions such as placental failure and other conditions with fetal circulatory impairment (e.g. fetal heart lesions). Doppler studies of the maternal uterine arteries are used to diagnose and monitor abnormal implantation (e.g. pre-eclampsia) in which failure of spiral artery conversion (see above) causes increased resistance evidenced by an abnormal diastolic 'notch'. Changes in the fetal circulation are mediated by increasing resistance in the umbilico-placental circulation and the resulting hypoxemia-acidemia. Cardiac afterload and output of the ventricles are affected differently because of the parallel arrangement of the fetal circulation (Baschat 2003): changes in right ventricular afterload are measured by changing resistance in the umbilical artery or descending aorta, while changes in left ventricular afterload are detected in the...
carotid or middle cerebral artery (MCA) resistance. Doppler measures of these changes allow assessment of circulatory redistribution.

These changes progress in a fairly predictable sequence through the different fetal vascular beds, starting with increasing umbilical artery resistance and followed by decreased middle cerebral artery resistance, the so-called ‘brain sparing’ effect described in 1986 by Wladimiroff (Wladimiroff et al. 1986). These resistance changes have opposite effects on the cardiac ventricles decreasing left ventricular afterload, while increasing right (systemic) ventricular afterload which manifests as reversal of flow across the aortic isthmus (Fournon et al. 1999). As right heart function deteriorates abnormal flow patterns appear in the fetal venous system, including preterminal development of abnormal ductus venosus waveforms (Rizzo et al. 1992; Hecher et al. 1995). These late venous changes coincide with the loss of fetal heart rate variability (Hecher et al. 2001): the left ventricular output also increases with increasing peak systolic velocity (Mari et al. 2007; al-Ghazali et al. 1989). Finally, with development of myocardial compromise and tricuspid dysfunction two ominous signs of imminent fetal demise appear, namely a sudden decrease in the MCA peak systolic velocity and pseudo-normalisation of MCA resistance (Senat et al. 2000).

The MCA is widely used as the site for measuring cerebral resistance but this practice has been questioned. Brain perfusion changes may be regionally heterogeneous and change during the progressive hypoxemia of placental failure. Several authors have suggested that the anterior cerebral artery resistance may be more sensitive, showing earlier vasodilation (Figueruela-Diesel et al. 2007; Dubiel et al. 2002; Benavides-Serralde et al. 2011; Benavides-Serralde et al. 2010). In addition, evidence of abnormal brain development measured by fetal MRI and MRS has been described in growth restricted infants despite normal MCA Doppler measurements (Sanz-Cortes et al. 2010). Newer techniques such as 3D-power Doppler analysis give a more comprehensive assessment of the fetal cerebral circulation (Bartha et al. 2009; Chang et al. 2003) and in fetal growth restriction appears to be more sensitive than MCA resistance alone (Bartha et al. 2009).

During the period of circulatory compensation and redistribution, the opposite systemic and cerebral resistance changes may occur concurrently. For this reason a cerebroplacental ratio (CPR; the ratio of cerebral resistance divided by uterine artery resistance) has been developed to track the circulatory changes. Changes in CPR are thought to reflect both ‘forced centralisation’ because of increased placental resistance and hypoxemia-induced vasodilation in the MCA (Baschat et al. 2002; al-Ghazali et al. 1989). Animal studies show that CPR is more sensitive to acute hypoxemia and better predictor of adverse outcome than the individual MCA or uterine artery resistances (Harrington et al. 1999; Bahado-Singh et al. 1999).

THE FETAL NEUROLOGICAL EXAMINATION – A WORK IN PROGRESS

The inaccessibility of the fetus to conventional neurological examination was until recently a fundamental obstacle to the development of fetal neurology as a discipline. Advances in neonatal critical care over the past five decades have resulted in major decreases in mortality among extremely preterm infants born at the brink of viability. This in turn allowed direct observation and study of the nervous system over an ex utero period equivalent to the late second and third trimesters of pregnancy. Unfortunately, these advances in survival came at the expense of significant neurodevelopmental burden among survivors. Recognition of this growing population of neurodevelopmentally impaired ex-preterm children activated a major movement to understand preterm birth-related brain injury and contributed significantly to the development of neonatal neurology as its subspecialty. Although these extremely preterm infants encounter a significantly different milieu from that experienced by normal, thriving in-utero fetuses they have provided an unprecedented window for understanding the immature brain and a vulnerability to injury. The large body of clinical and laboratory data amassed over time has provided an invaluable platform for understanding the in utero structural and functional development of the fetal brain. Many of the tools that facilitated the advance of neonatal neurology, especially neuroimaging, have been adapted to provide unprecedented access to the fetal brain.

The neurologist now has increasingly powerful imaging tools with which to examine the structural development of the fetal nervous system. First, fetal ultrasound and more recently fetal MRI have allowed detection of lesions with increasing resolution. The emergence of quantitative MRI for the fetal brain promises to take imaging beyond ‘pattern recognition’ and subjective lesion detection to more precise continuous measures of brain development (Limperopoulos et al. 2010; Limperopoulos and Clouchoux 2009). These techniques will allow close monitoring of global and regional volumetric development, microarchitectural fibre tract development and cortical gyration patterns (Clouchoux et al. 2012a; Mitter et al. 2011). Likewise, MRS has the potential to track patterns of important fetal brain substances (such as choline, creatine and N-acetyl aspartate) as well as the emergence of lactate, a potential marker of anaerobic metabolism (Berger-Kulemann et al. 2012). Doppler ultrasound has long been used by obstetricians to monitor the fetal circulation and measurements of resistance in the middle cerebral arteries are now routinely used to detect fetal ‘brain sparing’ in situations with potential fetal hypoxemia or hypoperfusion (Baschat et al. 2001).

Evaluation of fetal neurological function is less advanced than imaging of the fetal CNS anatomy. Crude measures of neurological function in high-risk patients include fetal movement counts, the development of polyhydramnios and assessment of fetal ‘tone’ in the biophysical profile (Manning 2009).
Direct observation of fetal movements including facial, ocular, oral and breathing movements by 3D and 4D ultrasound permits a gross evaluation of fetal motor activity and behavioural state (Kurjak et al. 2005) but these techniques have not been widely incorporated into clinical practice. An important gap in our diagnostic armamentarium is the lack of a readily accessible technique for measuring electrocortical activity from the maternal abdomen using fetal magnetoencephalography (Lowery et al. 2006) but at the present time this is an expensive, time-consuming and complex technique. Special frequency- and time-domain approaches to fetal heart rate variability may provide a window into the fetal autonomic system (Van Laar et al. 2008). For obvious reasons examination of the peripheral nervous system is currently not possible.

Resting state studies of fetal brain connectivity are being explored in research centres, based on the blood-oxygen-level dependent technique of MRI (Ferrazzi et al. 2014). Evoked responses have been used to test special senses in the fetus, including auditory evoked responses to a vibroacoustic stimulus as well as visual evoked responses to bright light projected across the abdomen of the mother (Lowery et al. 2006). An interesting approach to assess the fetal ability to mount an inhibitory influence from the cerebrum to the brainstem and spine is the testing for habituation during repeated sensory stimuli (Leader 1995): such tests require careful assessment of fetal behavioural state since this might significantly influence the results.

While there are major voids to be filled, particularly in evaluating neurological function in utero, these new insights and the advances in fetal diagnostics provide the neurologist with important tools to begin meaningful assessment of the fetal nervous system. This is done in close collaboration with fetal imaging specialists, obstetricians, perinatologists and geneticists among others; in some centres special fetal neuroradiology expertise has developed. Neurologists providing fetal counseling will need to develop an in-depth understanding of the normal and abnormal fetal milieu to include an understanding of maternal, placental and fetal conditions that may adversely affect the developing brain. Techniques previously developed by obstetricians and perinatologists to assess fetal well-being have included components that assess the fetal nervous system, as it is imperative that neurologists involved in fetal counseling become informed about the strengths and limitations of studies performed by the multidisciplinary fetal care team. Obstetricians in most developed countries perform routine screening tests at specific gestational ages, including the first trimester for accurate ultrasound dating of the pregnancy and to screen for aneuploidy and again toward midgestation when more detailed ‘anatomy’ ultrasound is performed. The technique of non-invasive prenatal testing performed on fetal genetic material obtained from the maternal circulation is in the early stages but has the potential to provide unprecedented insights into the genomic and epigenomic origins of fetal conditions. Tests for neural tube defects may be performed on maternal serum and confirmed by amniocentesis with tests of alpha-fetoprotein and cholinesterase levels: likewise, in patients affected by suspected fetal encephalitis special maternal serology studies, possibly followed by more direct testing in the amniotic fluid, may be performed. In high-risk pregnancies obstetricians and perinatologists utilise repeated tests such as the biophysical profile and the NST to monitor fetal well-being. The assimilation of this battery of neurodiagnostic techniques into the ‘toolbag’ of the neurologist permits not just the ability to counsel parents-to-be about diagnosis and prognosis but also allows for the development of rational plans for preventive brain-oriented care of the high-risk transitional period.

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# Neurological Diseases in the Perinatal Period

*Miriam Martinez-Biarge and Linda S de Vries*

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CHAPTER 2

Neurological Diseases in the Perinatal Period
Miriam Martinez-Biarge and Linda S de Vries

This chapter deals with the period that extends from the onset of labour – covering abnormal intrapartum events – to the end of the neonatal period, conventionally limited to the first 28 days after birth. Most of the neurological problems of this period arise during the first 10 days after birth. Intracranial haemorrhages and hypoxia–ischaemia dominate the neurology of the perinatal period, although it must be emphasised that they do not account for all the neurological problems of this period and that their predominance should not lead one to miss other important diagnoses such as metabolic and neuromuscular diseases, which are discussed in Chapters 9 and Chapters 24–26 respectively.

The pre- and perinatal periods are nowadays more often considered as a continuum rather than two separate entities. Indeed, prenatal factors such as fetal growth restriction, prenatal hypoxia of whatever origin, prenatal inflammation and preterm birth all play a considerable role in the determination of many perinatal disorders. The response of the central nervous system (CNS) to the stress of the birth process and adaptation to extrauterine challenges are also important.

The two major pathological conditions encountered in the perinatal period – haemorrhage and hypoxia–ischaemia – are not totally separate entities. They often coexist, and they share some common causes and precipitating factors. However, other mechanisms such as mechanical trauma or coagulopathies can provoke haemorrhage without hypoxia, and the pathology and mechanisms are sufficiently different to warrant separate description.

INTRACRANIAL HAEMORRHAGE IN THE TERM INFANT

The epidemiology of intracranial haemorrhage (ICH) in the term infant has changed considerably over the past three decades. The incidence of traumatic haemorrhage, mainly subdural in location, has markedly decreased as a result of improvement in obstetric practices.

Some of these ICHs are related to a complicated and often assisted delivery. Using routine magnetic resonance imaging (MRI) in a group of asymptomatic infants, subdural and subarachnoid haemorrhages were, however, not an uncommon finding (Whitby et al. 2004). Intraparenchymal haemorrhage is also occasionally traumatic in origin (Brouwer et al. 2010) but this type of lesion has also been detected on antenatal imaging, in some cases related to alloimmune thrombocytopenia or a mutation in the COL4A1 gene (de Vries et al. 2009). Spontaneous intraparenchymal haemorrhage of unknown cause has also been reported (Sandberg et al. 2001 Cole et al 2017). Intraparenchymal haemorrhage, especially thalamic haemorrhage, may be due to cerebral sinovenous thrombosis (CSVT) in association with intraventricular haemorrhage (IVH) (Wu et al. 2003). A germinal matrix–IVH (GMH-IVH) in term infants is uncommon. There is some dispute about the site of origin (Pagano et al. 1990). Most consider that these haemorrhages originate from the choroid plexus.

SUBDURAL HAEMORRHAGE

Pathogenesis
Subdural haemorrhage may result from the following: a tentorial tear with rupture of the straight sinus or the vein of Galen, or smaller afferent veins; occipital osteodiastasis with damage to the occipital sinus or cerebellar veins; a tear of the falk with involvement of the inferior sagittal sinus; or injury to the bridging veins between either the convexity of the hemispheres and the superior sagittal sinus, or the transverse or sigmoid sinus and the base of the brain (Govaert 1993; Volpe 2008). In the first two situations, the haemorrhage occurs in the posterior fossa, whereas in the other patients it is supratentorial, located adjacent to the convexity in case of injury to the bridging veins and the hemispheric fissure in falk laceration, and at the base of the brain with rupture of the veins draining into the lateral sinus.
Towne et al. (1999) looked at the effect of the mode of delivery in nulliparous women on neonatal intracranial injury. Rupture of the veins is caused by excessive head moulding in vertex presentation or excessive traction on the head presenting last in a breech presentation (Pape and Wigglesworth 1979). Towne et al. (1999) found that the rate of ICH was higher among infants delivered by ventouse extraction, forceps or Caesarean section during labour than among infants delivered spontaneously, but the rate among infants delivered by Caesarean section before labour was not higher, suggesting that the common risk factor for haemorrhage is abnormal labour. Recent MRI studies have shown that, when MRI is used routinely in term infants, a subdural haemorrhage, which tends to be small, was noted as a common finding (Whitby et al. 2004). In a study by Looney et al. (2007) a symptomatic ICH was found in 26% of 97 neonates following vaginal birth and in a study by Rooks et al. (2008), 46 of 101 asymptomatic infants showed a subdural haemorrhage, which tended to be small. According to these two studies the subdural haemorrhages will resolve within 4 weeks' and all had resolved by 3 months. They occur mostly in the posterior fossa or over the occipital lobes near the tentorium. This is in contrast to infants with non-accidental injury, who have subdural haematomas that are generally located in the interhemispheric fissure or over the cerebral convexities. Retinal haemorrhages are also often seen (20%–40%) in newborn infants and red blood cells are often found in their cerebrospinal fluid (CSF), all suggestive of mild trauma after vaginal birth (Holden et al. 1999).

Localised trauma with skull fracture by forceps application is rare. Tentorial haemorrhage can also occur as a consequence of ventouse extraction (Govaert 1993; Brouwer et al. 2010). A subdural haemorrhage associated with a frontal lobar haemorrhage without apparent trauma has also been reported (Fig. 2.1).

### Clinical Manifestations of Subdural Haemorrhage

The clinical features are variable depending on the location and acuteness of the haemorrhage. In acute cases of posterior fossa haemorrhage, there can be massive bleeding with compression of vital brainstem structures, manifested by stupor or coma, nuchal rigidity, opisthotonus, eye deviation, bradycardia and apnoeic spells. Seizures occur in 36% of cases (Govaert 1993). A tense fontanelle, generalised hypotonia, eye deviation, facial palsy and unequal pupils may be observed. Of the 90 infants reviewed by Govaert (1993), a fatal outcome occurred in 15 unoperated and three operated cases. Sequelae include hydrocephalus, but outflow obstruction can be temporary and managed by insertion of a subcutaneous reservoir into the lateral ventricle. In subacute cases, the onset of neurological symptoms is delayed for 12 hours or more. Irritability, stupor, a bulging fontanelle and respiratory irregularities may suggest the diagnosis. Diagnosis by ultrasound is possible, provided that the collection is large enough. Computed tomography (CT) and especially MRI give a better definition of the size and exact localisation of the haematoma, and MRI will give the best appreciation of associated ischaemia (Govaert 1993; Sandberg et al. 2001). Surgical treatment is effective but adhesions may evolve with development of hydrocephalus, requiring shunt insertion. In a study by Blauwblomme et al. (2013), 11 of 16 infants required neurosurgical interventions, with nine presenting within the first 24 hours with symptoms of brainstem dysfunction. One should also consider performing percutaneous needle aspiration.
to relieve the midline shift caused by the subdural haemorrhage, which was successfully performed in five of seven infants who required surgical decompression of the clot (Vinchon et al. 2005). Successful needle aspiration was also performed in two infants with haemophilia A (Peyre et al. 2008).

Supratentorial haematoma of the convexity does not usually produce an immediate dramatic clinical picture. In typical patients, focal seizures or asymmetry in tone, or both, occur on the second or third day after birth (Sandberg et al. 2001). The occurrence of a third cranial nerve palsy manifested by a dilated, non-reactive pupil on the side of the haematoma is characteristic. Minor subdural haematomas over the convexity may give only minimal clinical signs (Whitby et al. 2004). In cases of a subdural haemorrhage, the CSF is usually bloody. Lumbar punctures should no longer be used for the diagnosis of ICH, in view of the different imaging techniques now available.

Basal subdural haemorrhage caused by lateral tentorial injury results in collection of blood underneath the temporal lobe and/or occipital lobes. Govaert (1993) reviewed 21 cases confirmed by CT, which presented in a similar way to convexity haematomas. Such instances are sometimes associated with arterial ischemic stroke caused by compression of the middle cerebral artery (Govaert et al. 1992a). Similar cases have been reported involving the posterior cerebral artery (van der Aa et al. 2013a).

**Neurodevelopmental Outcome**

Outcome data tend to involve cohorts with a combination of different types of haemorrhages (supra- and infratentorial, subdural and intraparenchymal). Data is limited and the children have often been assessed at a young age. Taking this into account, outcome has been reported to be better than expected (Jhawar et al. 2005; Brouwer et al. 2010). Jhawar et al. (2005) studied 66 infants and reported that, overall, 57% of infants had no physical or cognitive deficits at follow-up. The most favourable outcomes occurred among those with subdural haemorrhage (80% had no disability). Brouwer et al. (2010) studied 53 infants and reported a mortality rate of 25% and a cerebral palsy (CP) rate of 8.6% among survivors. Of the 34 survivors without CP (88.2%), however, 30 had an early normal neurodevelopmental outcome in spite of often large, intraparenchymal haemorrhages. In the study of Blauwblomme et al. (2013) only two infants required a ventriculoperitoneal shunt and, with a mean follow-up of 7.8 years, two of their 16 infants showed a mild developmental delay and 1 had severe developmental delay.

**INTRACEREBELLAR HAEMORRHAGE**

Intracerebellar haemorrhage has many features in common with a subdural haematoma in the posterior fossa. Its mechanism is different and it seems to be related to hypoxia and ischaemia rather than to mechanical trauma, although it may be caused by occipital osteodiastasis or traumatic cerebellar injury (De Campo 1989). Neurological manifestations are generally overshadowed by signs of hypoxia–ischaemia or respiratory distress. Apnoea, bradycardia and a fall in haematocrit are frequent features. Obstructive hydrocephalus is common even after surgical evacuation of the collection, and may be associated with the development of a cerebellar cyst communicating with the fourth ventricle (Huang and Shen 1991). Clinically, cerebellar dysfunction may be seen as sequelae (Williamson et al. 1985). Cerebellar haemorrhage has also been seen as a complication of extracorporeal membrane oxygenation (Bulas et al. 1991), coagulopathy and in some infants with organic acidurias (Dave et al. 1984) (Fig. 2.2).

**INTRAPARENCHYMAL HAEMORRHAGE**

Intraparenchymal haemorrhage is virtually always associated with subarachnoid haemorrhage. In most cases it involves a single lobe and may result from trauma or haemorrhagic infarction (Huang and Robertson 2004; Jhawar et al. 2005; Brouwer et al. 2010, Cole et al 2017) (Fig. 2.2). Breech delivery and mechanically difficult deliveries in general, were a major causal factor, although intraparenchymal haemorrhage...
has also been reported in uncomplicated vaginal deliveries (Sandberg et al. 2001; Brouwer et al. 2010). Clotting defects and especially neonatal allo- and rarely isoimmune thrombocytopenia, may play an auxiliary role (Berkowitz et al. 2006). The symptomatology resembles that of a subdural haematoma (Govaert 1993), with a symptom-free period of sometimes more than 24 hours, followed by focal signs and symptoms of raised intracranial pressure. Variable focal signs depend on the lobe involved and may include convulsions, asymmetry in tone and ocular signs. Surgical evacuation is indicated when symptoms of increased intracranial pressure are present, associated with a midline shift on neuroimaging (see Fig. 2.1). A residual cavity in the brain may not cause any symptoms or may be associated with a focal deficit (Brouwer et al. 2010). A similar picture may be seen with haemorrhagic brain infarction (Bruno et al. 2014, Cole et al. 2017).

Haemorrhagic disease of the newborn should no longer be seen with prophylactic administration of vitamin K, but is still reported in the literature in countries where prophylaxis is not yet common practice or in infants with specific problems such as α1-antitrypsin deficiency, Alagille syndrome and other problems leading to malabsorption of orally administered vitamin K (Vorstman et al. 2003; Danielsson et al. 2004; Ijland et al. 2008; Yilmaz et al. 2009). Differences in vitamin K prophylaxis regimens have shown that a daily dose of 25mcg vitamin K fails to prevent haemorrhages in apparently healthy infants with unrecognised cholestasis because of biliary atresia. Oral prophylaxis of 1mg weekly offered significantly better protection to these infants and was of similar efficacy to 2mg of intramuscular prophylaxis at birth (van Hasselt et al. 2008).

Other coagulation disorders may be responsible for severe ICH in the neonatal period. Haemophilia can cause subdural intraparenchymal haemorrhage, subgaleal haemorrhage or IVH (Chalmers 2004).

Brainstem haemorrhage is rarely of traumatic origin. At least one patient with spontaneous brainstem haemorrhage, with diaphragmatic paralysis and lower cranial nerve involvement, is on record (Blazer et al. 1989).

**THALAMIC HAEMORRHAGE**

Thalamic haemorrhage (Fig. 2.3) is a rare form of neonatal intraparenchymal haemorrhage (Trounce et al. 1985; de Vries et al. 1992b). The haemorrhage can be associated with an IVH (Roland et al. 1990; Govaert 1993; Monteiro et al. 2001; Wu et al. 2003) or limited to the thalamus and neighbouring structures. It was first shown by Wu et al. (2003) that a sinusvenous thrombosis should be suspected when the thalamic haemorrhage is associated with an IVH. With increased use of MRI and MR venography (MRV) the association of a thalamic haemorrhage caused by a thrombosis of the straight sinus is now well recognised (Kersbergen et al. 2013) (Fig. 2.3). Some venous congestion in the periventricular white matter or even venous infarction can be present on the side of the thalamic haemorrhage. With power Doppler through the anterior, posterior, and mastoid fontanelle, or with better imaging such as CTV or MRV, one can confirm the venousous thrombosis. Once confirmed, some will consider the use of anticoagulants, usually low-molecular-weight heparin, but others are less inclined to treat in the presence of an associated parenchymal haemorrhage (Jordan et al. 2010; Moharir et al. 2010). Although the course may appear favourable in early infancy, Monteiro et al. (2001) reported that epilepsy with continuous spike waves during sleep (ESES) was related to primary neonatal thalamic
haemorrhage. In a review of the literature they reported occurrence of epilepsy in 13 of 28 infants. Kersbergen et al. (2013) were able to confirm this observation in 15 infants with a thalamic haemorrhage associated with a thrombosis of the straight sinus. Of the 15 infants, three developed ESES (spike and wave index [SWI] >85%) between age 2 and 9 years, a further two children had ESES spectrum disorder (SWI between 50% and 85%), and in two more significant sleep-induced epileptiform activity (SIEA) was noted (SWI between 25% and 50%). Two other children were diagnosed with focal epilepsy, in the absence of sleep-induced epileptiform EEG abnormalities. A routine sleep EEG is therefore recommended in infants with a thalamic haemorrhage to make the diagnosis before a decline in cognitive and language performance occurs. Unilateral thalamic haemorrhage should not be confused with the more severe condition of bilateral thalamic and basal ganglia involvement in term infants with ‘near-total acute asphyxia’ (Barkovich 1992; Rutherford et al. 1995; Miller et al. 2005), which can in rare cases also be haemorrhagic (Kreusser et al. 1984).

**PRIMARY SUBARACHNOID HAEMORRHAGE**

It is common to see haemorrhage within the subarachnoid space, not as an extension from an intraventricular, subdural or intraparenchymal haemorrhage, based on the fact that bloody or xanthochromic CSF is frequently found when performing a lumbar puncture during the first few days after birth. A significant subarachnoid haemorrhage, also visible on CT or MRI, is much less common. Subarachnoid haemorrhage can be either traumatic or related to asphyxia. These were found, respectively, in 16 and 17 of 48 cases reported by Govaert (1993), whereas 10 cases remained of undetermined origin.

Clinical manifestations are often lacking. In some, irritability and seizures, occasionally presenting as apnoeic spells, are noted, typically on the second day after birth in otherwise well infants (Volpe 2008). Limited outcome data are variable. According to Palmer and Donn (1991), only 50% of the infants were neurologically normal, regardless of whether the presumed aetiology was hypoxic–ischaemic or traumatic. Others report a favourable outcome, although development of posthaemorrhagic ventricular dilatation can occur. Diagnosis is difficult using ultrasound unless the posterolateral window is used. MRI is a better imaging modality, showing blood in the posterior interhemispheric fissure and the region of the vein of Galen, and on the tentorium (Paneth et al. 1994). These studies were performed using ultrasound or CT; associated hypoxic–ischaemic lesions may not have been noticed and may have played an important role in the outcome.

**EPIDURAL HAEMATOMA AND RARE TYPES OF NEONATAL INTRACRANIAL HAEMORRHAGE**

Epidural haematoma is a rare condition in newborn infants and is usually caused by mechanical trauma during or sometimes after delivery, by a fall at home or out of an incubator in the neonatal intensive care unit (Vachharajani and Mathur 2002).

Cephalhaematoma is commonly associated and communicates with the extradural blood collection through a skull fracture. Signs of progressive CNS dysfunction are usually delayed and may be absent altogether. Ultrasonography is not very helpful, and the diagnosis is usually made by CT or MRI. Surgical evacuation is sometimes indicated but needle aspiration of the epidural haematoma has also been reported (Vachharajani and Mathur 2002). The collection tends to rapidly liquefy, leading to a differential density. Conservative treatment is possible in asymptomatic infants and those with just mild symptoms.

Other rare types of haemorrhage in the newborn infant include subgaleal haemorrhage with extensive blood loss (Kilani and Wetmore 2006; Swanson et al. 2012), haemorrhages related to vascular malformations such as Osler–Weber–Rendu (Morgan et al. 2002; Delaney et al. 2012), the vein of Galen (Chapter 15) and congenital tumours.

**GERMINAL MATRIX–INTRAVENTRICULAR HAEMORRHAGE IN THE PRETERM INFANT**

**Pathogenesis**

This type of haemorrhage is especially common in the very-low-birthweight infant. Germinal matrix-intraventricular haemorrhage (GMH-IVH) mainly occurs within the first 3 days after delivery and is rarely noted to develop beyond the first week after birth, in contrast with white matter injury (see below). The haemorrhage develops in the germinal matrix and may subsequently rupture into the lateral ventricle. IVH is less common in the term infant and is then more likely to start off in the choroid plexus, rather than the germinal matrix, which has shown almost complete involution at term equivalent age. With routine use of cranial ultrasonography, the incidence could be assessed and was approximately 40% in the early 1980s, and has decreased to about 20% in the 1990s (Papile et al. 1978; Heuchan et al. 2002; Horbar et al. 2002). Less mature infants are more at risk of developing a haemorrhage, and it was shown by Perlman and Volpe (1986) that 60% of infants weighing <1000g at birth developed GMH-IVH, compared with only 20% of larger very low birth weight infants (Fig. 2.4). In a more recent study by Horbar et al. (2012), only the change in severe GMH-IVH grades III and IV was reported for preterm infants with a birthweight of 500–1500g. The decrease in severe IVH was of borderline statistical significance ($P = 0.04$) and stabilised at around 6%.
In a population-based study in France, a decline from 24.9% in 2005 to 12.4% in 2010 was reported, but the decrease was only significant for grade I haemorrhage (Pinto Cardoso et al. 2013). The average incidence for intraparenchymal haemorrhage reported in the literature is between 5% and 11% (de Vries et al. 2004). A lower incidence of 3% was reported in a French population-based cohort (Larroque et al. 2003). No statistically significant decline was noted in our own population for severe GMH-IVH, between 1991 and 2006, but a significant decline was seen for cystic periventricular leukomalacia (c-PVL) (Groenendaal et al. 2010).

The precise nature and origin of GMH-IVH remains uncertain. Although some groups have suggested that the capillaries in the germinal matrix do not rupture easily, others have claimed that this can result from the fact that the vessels are immature in a structure with little evidence of basement membrane protein (Grunnet 1989). Pape and Wigglesworth (1979) suggested from their injection studies that capillary bleeding was more prominent than terminal vein rupture. Anatomical analysis of the developing cerebral vasculature was unable to show precapillary arteriole-to-venous shunts (Anstrom et al. 2002). Most instances of GMH-IVH in preterm infants originate in the subependymal germinal matrix, the highly cellular area that gives rise to neurons and glia and involutes before term. In infants <28 weeks’ gestational age, haemorrhage is often located in that part of the matrix overlying the body of the caudate nucleus, whereas in those >28 weeks it more commonly overlies the head of the caudate (Anstrom 2002; Del Bigio 2011). Haemorrhages usually arise in the region of the germinal matrix. The venous architecture can be visualised with a recently introduced MRI sequence, susceptibility weighted imaging (SWI) (Tortora et al. 2016) IVH results when the ependyma ruptures. Parenchymal haemorrhage, still often referred to as grade IV haemorrhage, was initially considered to be an extension of the haemorrhage with rupture of the ependyma. It is now considered more likely to be due to impaired drainage of the medullary white matter veins (Takashima et al. 1986; Gould et al. 1987), and the terms ‘venous infarction’ and ‘periventricular haemorrhagic infarction’ (PVHI) appear to be more appropriate. Various grading systems have been devised (Papile et al. 1978; Volpe 2008). The grading system according to Volpe is shown in Table 2.1. It is preferable to use a separate notation for associated (haemorrhagic) lesions in the white matter, rather than the term ‘grade IV haemorrhage’. A PVHI is often noted to develop following an IVH, which may lead to impaired venous drainage into the terminal vein. The lesion is mostly unilateral and on the side of the IVH. It is important to note both the site and the extent of the lesion (Rademaker et al. 1994; de Vries et al. 2001; Bassan et al. 2006). Most of the parenchymal lesions will develop in the parietal white matter, but some occur in the frontal white matter or the germinal matrix of the temporal white matter (Soltirovska Salamon et al. 2013)(Fig. 2.5).
Other associated lesions that have mainly been diagnosed at post-mortem examination include pontine neuronal necrosis, encountered in 46% of cases, which were associated with pontosubicular necrosis in 20% (Armstrong et al. 1987).

Risk Factors
Risk factors can be prenatal, intrapartum or neonatal in origin.

Prenatal Risk Factors
Histological signs of amniotic infection have been shown to increase the risk of GMH-IVH. Increased serum levels of interleukin (IL)-1β, IL-6 and IL-8 have been found to be associated with severe IVH in extremely preterm infants (Yanowitz et al. 2002; Heep et al. 2003; Tauscher et al. 2003). In the study by Yanowitz et al. (2002), a correlation was shown between blood cytokine concentrations and altered haemodynamic function with cord blood IL-6 concentration correlating inversely with newborn systolic, mean and diastolic blood pressures. Maternal pre-eclampsia has been associated with a reduced risk of GMH-IVH (Shankaran et al. 1996; Gagliardi et al. 2013). The protective effect appears to be due to enhanced in utero maturation of the fetus. Administration of antenatal corticosteroids is, according to several studies, the most important protective factor against the development of GMH-IVH (Shankaran et al. 1996). This may be due to a direct maturational effect on the brain, but other factors may also be involved, such as the reduction of the severity of lung disease and the decreased need for inotropes. Several studies have shown that male sex is associated with a higher incidence of IVH and an increased rate of severe IVH (Mohamed and Aly 2010; Kent et al. 2012).

Intrapartum Risk Factors
There is still no agreement about the effect of the mode of delivery on the occurrence of GMH-IVH. A reduced mortality but not a reduced risk of a GMH-IVH was reported in a Swedish population-based study of preterm infants with a gestation of 25–36 weeks, when avoiding vaginal breech delivery (Herbst and Källén 2007). In a cohort study, a protective effect of a Caesarean section was seen only for the most immature infants (<27 weeks’ gestation) (Thor et al. 2001). A vaginal breech delivery is in some studies associated with a higher risk of a large GMH-IVH, but this effect was lost in a multivariable analysis (Riskin et al. 2008; Shankaran et al. 1996). Neonatal transport for infants born outside a tertiary centre has also been shown to be a risk factor (Mohamed and Aly 2010). It was recently suggested that it might not be the transport itself but the association with underlying clinical variables (Watson et al. 2013). Being born during the night was also reported with an increased risk for development of a GMH-IVH. Off-peak hour delivery was associated with increased odds of severe IVH among survivors (OR 1.39, 95% CI 1.23-1.57) and the composite outcomes of death or severe IVH (OR 1.16, 95% CI 1.07-1.25) and death or major morbidity (OR 1.08, 95% CI 1.02-1.15). (Jensen and Lorch 2017.)

Neonatal Risk Factors
Respiratory problems, and respiratory distress syndrome (RDS) in particular, have been recognised as important risk factors in the development of GMH-IVH. This association is most probably not causal but related to the concomitant complications occurring during mechanical ventilation for RDS, such as hypercapnia, pneumothorax and acidosis (Kaiser et al. 2006; Vela-Huerta et al. 2009). As a result of improvement in ventilatory techniques, including an increased use of nasal continuous positive airway pressure, hypercapnia and severe acidosis have become less common. It has been noted that hypercapnia, a potent cerebral vasodilator, especially when combined with a severe acidosis, is associated with GMH-IVH (Vela-Huerta et al. 2009). Postnatal administration of surfactant has also led to less severe RDS, with fewer complications such as pneumothorax and a decrease in the duration of mechanical ventilation. Haemodynamic factors play an important role. The immature brain is considered vulnerable to fluctuations in blood pressure caused by limitations in autoregulation of

<table>
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<tr>
<th>Table 2.1 Staging system for germinal matrix–intraventricular haemorrhage (GMH-IVH)</th>
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<tr>
<td>Description</td>
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<tr>
<td>Grade I: germinal matrix haemorrhage or minimal IVH (&lt;10% of the ventricular area on the parasagittal plane)</td>
</tr>
<tr>
<td>Grade II: intraventricular haemorrhage without ventricular dilatation</td>
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<tr>
<td>Grade III: intraventricular haemorrhage with acute ventricular dilatation (clot fills &gt;50% of the ventricle, best seen on parasagittal view)</td>
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<tr>
<td>Intraparenchymal lesion (IPL) – describe size, location</td>
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Figure 2.5 Preterm infant, gestational age 33 weeks. (a) Axial T2-weighted sequence at 1 week shows an intraventricular haemorrhage with associated parenchymal haemorrhage (venous infarction) in the temporal lobe. (b) The optic radiation on the left side cannot be visualized with diffusion tensor imaging at term-equivalent age.
cerebral blood flow (CBF) (Lou 1988). Impaired autoregulation renders the cerebral circulation ‘pressure passive’ and hence unprotected from any wide swings or changes in blood pressure. This applies especially to sick preterm infants. An increase in systemic pressure can probably produce rupture of capillaries (Perlman et al. 1983; Miall-Allen et al. 1989), which could probably occur if a period of hypotension and ischaemia, with injury of the germinal matrix vessels, precedes the peaks of hypertension. The fluctuating pattern may be exaggerated in hypovolaemia (Pryds 1991). Using near-infrared spectroscopy (NIRS), it was shown that routine caregiving procedures in critically ill, preterm infants are associated with major circulatory fluctuations and that these cerebral haemodynamic changes were associated with early parenchymal ultrasound abnormalities (Limperopoulos et al. 2008). Hypotension is common in infants with severe RDS and, in the presence of a pressure-passive cerebral circulation, may lead to hypoxia–ischaemia of the germinal matrix. It has been shown that arterial hypotension precedes the development of GMH-IVH, with the haemorrhage occurring during a period of reperfusion (Vela-Huerta et al. 2009). Osborn et al. (2003) showed a low flow in the superior vena cava, detected during the first few hours of life, preceding an IVH. In a study using continuous NIRS and mean arterial blood pressure (MABP) measurements, MABP–regional cerebral oxygen saturation (rScO₂) correlation suggested more blood pressure-passive brain perfusion in infants with an IVH (Alderliesten et al. 2013). A reduction in GMH-IVH has been seen during an era of closer attention to blood pressure, gentle handling, synchronous ventilation, less need for invasive respiratory support and less severe RDS, because of antenatal steroid and postnatal surfactant therapy, rather than any specific drug used as prophylaxis.

Thrombophilic disorders, including the factor V Leiden mutation, which renders factor V resistant to cleavage by activated protein C, and the prothrombin G20210A mutation, which was found to be associated with raised plasma concentrations of prothrombin, were suggested to play a role in the development of GMH-IVH (Ryckman et al. 2011). In preterm infants with an atypical time of onset, either antenatal or beyond 96 hours after birth, an association was noted with polymorphism in the factor V Leiden gene (Harteman et al. 2012a; Ment et al. 2014). Aden et al. (2013) analysed genotypes for seven genes from 224 unborn preterm neonates, treated with antenatal steroids, and with grade III–IV IVH and 389 matched controls. They found methylenetetrahydrofolate reductase (MTHFR) to be more prevalent only in infants with grades III and IV haemorrhage compared with 389 matched controls. In smaller studies, the IL-6 CC genotype had been noted to increase the risk of developing severe haemorrhagic lesions and an impairment of cognitive outcome, according to some but not others (Harding et al. 2005; Göpel et al. 2006). Antenatal porencephaly has been reported to be associated with a mutation in the collagen 4A1 and 4A2 gene (COL4A1, COL4A2) encoding procollagen type 4a1, a basement membrane protein, in two preterm siblings and preterm twins (de Vries et al. 2009; Bilguvar et al. 2009). The diagnosis of a COL4A1 mutation can be made before birth and should be considered in the presence of a parenchymal haemorrhage associated with a cerebellar haemorrhage (Lichtenbelt et al. 2012). A mutation in the collagen 4A2 gene may result in the same imaging abnormalities (Verbeek et al. 2012).

Cerebellar Haemorrhage

The cerebellum is rapidly developing (fivefold increase in volume between 24 and 40 weeks’ corrected age), and may therefore be especially vulnerable (Chang et al. 2000). Injury to the cerebellum is often related to cognitive and behavioural deficits later in life (Limperopoulos et al. 2007; van Kooij et al. 2012 Ranger et al 2015). Primary cerebellar haemorrhage (CBH) in preterm infants may originate in the external granular layer, from the germinal matrix that is present in the subependymal region around the fourth ventricle. The vulnerable capillaries, present in these structures, can easily rupture, especially with the circulatory changes in the vulnerable preterm infant (Volpe 2009). The possible role of bands used for fixation of facemasks has in the past been suggested as a cause, but this appears unlikely because the incidence was found to be similar when masks were not applied (Paneth et al. 1994).

Neuroimaging Findings

This type of haemorrhage appears to occur more often in the very immature preterm infant with a gestational age <28 weeks’ (Limperopoulos et al. 2005; Steggerda et al. 2009). Ultrasonography, especially when performed through the mastoid fontanelle as the acoustic window, can be diagnostic when the lesion is at least 4mm in diameter (Steggerda et al. 2009). The lesion may be unilateral or bilateral, large or punctate, and may also affect the vermis (Limperopoulos et al. 2005; Ecury-Goossen et al. 2010) (Fig. 2.6). It is often associated with a supratentorial IVH. The incidence varies between 3% and 9%, when using cranial ultrasonography, including the mastoid fontanelle (Limperopoulos et al. 2005), but was reported as 15% in a more recent cohort (Steggerda et al. 2009). When using MRI the incidence increases dramatically and can be as low as almost 20%, mainly as a result of recognition of punctate lesions, which are a much more common finding in the extremely preterm infant, but are less likely to be associated with severe adverse neurological sequelae (Tam et al. 2011a). Steggerda et al. (2013) diagnosed these small CBHs on routine term equivalent age (TEA) MRI in 16 of 108 very preterm infants (<32 weeks’ gestation). In this study low-frequency oscillation ventilation and severe IVH were recognised to be independent risk factors of small CBHs. There was no association between small CBHs and neurodevelopmental outcome at 2 years of age. Besides the actual lesion in the cerebellar tissue, there are additional deleterious effects such as the toxicity of blood breakdown products.
such as haeme and iron in the CSF as a result of (supratentorial) haemorrhage. This iron accumulation and free radical attack have been associated with cerebellar atrophy (Tam et al. 2011b) (Fig. 2.7). In several studies, where MRI was not used routinely, cerebellar atrophy, as well as atrophy of the pons, has been reported as a common sequela of severe immaturity. It is likely that the atrophy was preceded by a cerebellar haemorrhage in the neonatal period (Bodensteiner and Johnsen 2005; Johnsen et al. 2005; Messerschmidt et al. 2005; Srinivasan et al. 2006; Tam et al. 2011b; Fumagalli et al. 2015).

Diagnosis and Clinical Manifestations

The onset of GMH-IVH has been noted to occur earlier in preterm infants weighing <1000g than in larger ones. Perlman and Volpe (1986) found that the onset in such infants was 10±8 hours, as opposed to the second or third day in larger infants. Clinical symptoms are not too common and the diagnosis is most often made using routine cranial ultrasonography. With increased use of MRI, including the use of SWI we are aware that ultrasonography is less accurate in less severe GMH-IVH, and may miss a small IVH or a germinal matrix haemorrhage in areas distant from the caudate groove, e.g. in the temporal lobe. Electroencephalography (EEG) is not particularly helpful in making the diagnosis, although a change in the background pattern may precede the development of an IVH (Alderliesten et al. 2013; Noori et al. 2014).

Three clinical syndromes can be recognised in preterm infants not paralysed or heavily sedated on the ventilator (Volpe 2008). The first is known as catastrophic deterioration, noted by a sudden deterioration in the infant’s clinical state, e.g. an increase in oxygen or ventilatory requirement, a fall in blood pressure and/or acidosis. The fontanelle may be tense or even bulging, and clinical seizures may be noted. More often, however, a drop in haematocrit is seen without a clear change in the infant’s condition. The saltatory syndrome is more common and gradual in onset, presenting with a change in spontaneous general movements. The third and most frequent presentation is asymptomatic: 25–50% of infants with GMH-IVH have no obvious clinical signs. On careful neurological assessment, impaired clinical signs, such as visual tracking and later development of roving eye movements, a tight popliteal angle, and a decrease in tone and poor motility have been shown to correlate with GMH-IVH (Dubowitz et al. 1981). Motor agitation was noted to precede the diagnosis of a cerebellar haemorrhage (Ecury-Goossen et al. 2010).

Course and Sequelae

With ultrasonography largely available in neonatal units, most low-risk, preterm infants have a routine ultrasound scan soon after admission, or within the first few days after birth, rather than a full neurological assessment. GMH-IVH may already be present on the first ultrasound examination, performed soon after admission, and 90% of infants with the condition controls (Olischar et al. 2007). In another study the number of bursts per hour counted on the continuous amplitude-integrated EEG was found to be helpful with regard to prognosis (Hellström-Westas et al. 2001). Using continuous NIRS, several studies have been able to show lower rcSO2 and higher cerebral fractional oxygen extraction values before the development of an IVH (Alderliesten et al. 2013; Noori et al. 2014).
can be detected by the fourth day after birth (Volpe 2008). The haemorrhage tends to reach its maximal extent within 3–5 days of diagnosis and it is rare to see the development of a GMH-IVH beyond the end of the first week.

The course is rarely fatal and death may follow redirection of care in view of a poor prognosis, especially when there is bilateral parenchymal involvement (Maitre et al. 2009). This decision is usually not based just on cranial ultrasonography, but takes other factors into account such as the aEEG background activity, the neurological assessment and the presence of seizures. The mortality rate among 214 preterm infants with a large intraventricular haemorrhage (grade III) or PVHI seen in Utrecht was 33% (Brouwer et al. 2008).

Once the diagnosis is made, sequential examinations are recommended to assess the evolution of the haemorrhage. When the haemorrhage is restricted to the germinal matrix (grade I) one can see subsequent development of a germinal matrix cyst. These cysts tend to resolve over the next 3–6 months and appear to be of little clinical consequence according to some (Payne et al. 2013), but not others (Bolisetty et al. 2014). This might be explained by destruction of neuron and glial cell precursors, which will have consequences on subsequent brain development (Del Bigio 2011).

Posthaemorrhagic ventricular dilatation (PHVD) and infantile hydrocephalus are an important sequel of a usually severe GMH-IVH. PHVD is considered to be caused by adhesive arachnoiditis. It is more common in infants who had a large haemorrhage, where blood has passed through the aqueduct and the foramina of Luschka and Magendie into the basal cisterns (Fig. 2.8). Acute outflow obstruction is less common but does occur, and is usually caused by a clot obstructing the aqueduct. PHVD may occur shortly after a large IVH, due to a large obstructing clot, but it is more common to see the development over the next 7–14 days. Having a large IVH is an indication for sequential ultrasound examinations, because it is well known that the larger the haemorrhage the higher the risk of developing PHVD (Brouwer et al. 2008). Without sequential ultrasound examinations, severe ventricular dilatation can be missed, since it can develop without any clinical symptoms or a rapid increase in head circumference, because the extracerebral space is large in the very preterm infant (Ingram et al. 2014). Once it has been recognised that the ventricles are starting to enlarge, the baseline size should be assessed using advanced volumetric three-dimensional MRI, showing an increase in both cortical grey and myelinated white matter.

Figure 2.8 Compression ultrasonography: (a) coronal and (b) midsagittal views performed 2 days after birth. MRI was performed a day later: (c) axial and (d) midsagittal T2-weighted sequences. A large intraventricular haemorrhage is seen in the ventricles, with associated enlargement of the third and fourth ventricles and involvement of the basal ganglia (right side). Also note the lack of extracerebral space on MRI, with low signal intensity of the occipital white matter and lack of cortical folding resulting from increased pressure.

index graph of Levene has an age range between 27 and 40 weeks. New reference values for the ventricular index and anterior and posterior horn widths were published with an age range between 24 and 42 weeks (Brouwer et al. 2012).

In a study by Murphy et al. (2002), a total of 248 very-low birthweight infants had a GMH-IVH (all grades) and a quarter of these developed PHVD. Spontaneous arrest was seen in 38%. Of the remaining 62%, 48% required non-surgical therapy, whereas 34% required surgical intervention and 18% died. In a more recent study of 208 preterm infants with a severe IVH (grade III/PVHI) from our own centre, 195 (94%) developed PHVD after IVH grade III or IV (VI >p97). Temporary treatment with lumbar punctures and punctures from a ventricular reservoir was sufficient for most of the infants. A ventricular reservoir was inserted in 135 infants (65%) and 47 of 196 survivors (24%) eventually required a ventriculoperitoneal shunt (Brouwer et al. 2015).

Raised CSF pressure can cause symptoms, including visual disturbance, seizures, feeding intolerance and apnoea. Short-term adverse effects on the nervous system have been confirmed using somatosensory and visual evoked potentials, Doppler estimates of cerebral blood flow velocity and NIRS (Soul et al. 2004; van Alfen et al. 2007; Klebermass-Schroefer et al. 2013). Soul et al. (2004) showed a pronounced effect of CSF removal on cerebral perfusion, irrespective of the opening pressure and the amount of fluid removed. The impact of removal of CSF on cerebral tissue was also assessed using advanced volumetric three-dimensional MRI, showing an increase in both cortical grey and myelinated white matter.
volume (Hunt et al. 2003). Jary et al. (2012a) performed measurements of intraventricular echodensity area and found that this correlated with motor outcome in infants with a parenchymal haemorrhage. Neither ventricular area nor ventricular width correlated with developmental outcome in those with a grade III IVH. In another study by the same group, using manual segmentation of brain volumes, the authors noted that brain growth is significantly impaired in PHVD and that total cerebral and cerebellar volume, measured at TEA, strongly related to both motor and cognitive outcome measured with the Bayley Scales of Infant Development, second edition (BSID-II) at 2 years of age. It was noted that CSF hypoxanthine levels, transforming growth factor-beta 1, soluble Fas levels were raised in infants with PHVDs, especially so in those with associated periventricular leukomalacia (Felderhoff-Mueser et al. 2003; Heep et al. 2004 Schmitz et al. 2011).

In spite of all these data, there is no direct evidence that early drainage of CSF alters the natural history or outcome of PHVD. In several retrospective studies early intervention of PHVD appeared to be associated with a better outcome and a reduced need for a ventriculoperitoneal shunt (de Vries et al. 2002; Brouwer et al. 2008; Bassan et al. 2012). A prospective randomised controlled trial allocating the infants to early versus later insertion of a subcutaneous reservoir has recently stopped enrolling patients (ISRCTN43171322) but the results have not been published yet. The initial data of the drainage intervention fibrinolytic therapy (DRIFT) study showed a reduced need for shunt insertion, 22% versus around 60% in the ventriculomegaly and acetazolamide multicentre studies (Whitelaw et al. 2003), but this reduction was not confirmed in the subsequent randomised controlled trial, with a large number of secondary IVHs in the group allocated to DRIFT (Whitelaw et al. 2007). No significant differences were seen across the 34 infants allocated to DRIFT and the 36 treated by tapping of CSF by reservoir. Among the survivors, 11 of 35 (31%) in the DRIFT group had severe cognitive disabilities (defined as severe sensori the survivors, 11 of 35 (31%) in the DRIFT group had severe cognitive and cognitive disability (<55 on the BSID-II) versus 19 of 32 (59%) in the standard group (adjusted odds ratio [OR]: 0.17 [95% confidence interval or CI: 0.05–0.57]).

Neurodevelopmental Outcome

Development of neurological sequelae depends mainly on the severity of the initial haemorrhage and on involvement of the periventricular white matter. Several studies (van de Bor et al. 2004; Bolisetty et al. 2014) have shown that even infants with a small GMH-IVH have a higher incidence of disability than those without. In a recent study by Vohr et al. (2014), after preterm birth and a grade II IVH, preterm adolescents were found to be at increased risk of learning challenges, including cognitive and executive function deficits, even after exclusion of those adolescents with associated periventricular haemorrhage. A large study from Australia reported outcome on a cohort comprising more than 2000 preterm infants, with 515 (21.3%) infants with a grade I–II GMH-IVH, diagnosed with cranial ultrasonography. They found increased rates of sensory impairment, developmental delay, CP (10.4%) and deafness at 2–3 years corrected age in those with a grade I–II GMH-IVH. The CP rate was also quite low (6.8%) in those without cranial ultrasonography abnormalities (Bolisetty et al. 2014). Another recent study (Payne et al. 2013) did not confirm these observations, which were based on ultrasound findings and may have missed associated white matter lesions and/or cerebellar haemorrhage. Vasileiadis et al. (2004) showed a 16% reduction in cortical volume at near term age in 23 preterm infants with an uncomplicated IVH. Kuban et al. (1999) noted that ventriculomegaly after a small haemorrhage was associated with a worse outcome, but this is more likely to be the result of associated white matter lesions, which probably play a more important role in determining outcome than a haemorrhage that is restricted to the lateral ventricle. The outcome of infantile hydrocephalus (PHVD with the need for a ventriculoperitoneal shunt) in preterm infants with a gestational age <33 weeks’ was reported by Persson et al. (2005, 2006), showing that although the prevalence came down to six per 1000 livebirths, 88% of these infants went on to develop CP. The outcome of infants with parenchymal haemorrhage depends very much on the size and in particular the site of the lesion (de Vries et al. 2011; Jary et al. 2012b). The mortality rate in a series reporting the outcome of large parenchymal haemorrhages is low and varies between 37% and 84% (Larroque et al. 2003; Futagi et al. 2006; Brouwer et al. 2008). Development of a single large porencephalic cyst after a large globular parenchymal haemorrhage is not so common any more. In our experience, multiple small cysts after a more triangular-shaped haemorrhage, which is not or only partly communicating with the lateral ventricle, are more often seen nowadays, and the outcome appears to be better. Of 76 infants found to have a unilateral intraparenchymal lesion >1cm in diameter, 39 (51%) did not have any motor sequelae at all at follow-up (Brouwer et al. 2008). Early prediction of hemiplegia is now possible, using MRI at 40–42 weeks’ postmenstrual age (Cowan and de Vries 2005; de Vries et al. 2011). At term, myelination should be present in the posterior limb of the internal capsule; infants who had asymmetry or lack of myelination in the posterior limb of the internal capsule at term went on to develop hemiplegia (de Vries et al. 1999). Diffusion tensor MRI can be used to visualise the tracts at an even earlier stage and motor outcome can already be predicted on an early MRI performed within the first 4 weeks’ after birth (Arichi et al. 2014; Roze et al. 2015).

Prevention

The increasing frequency of GMH-IVH in most centres is difficult to attribute to one single factor. Administration of antenatal corticosteroids is, according to several studies, the most important protective factor for development of GMH-IVH (Shankaran et al. 1996; Brownfoot et al. 2013). The effect may be due to a direct maturational effect on the brain,
but other factors may also be involved, such as the reduction of the severity of lung disease and the decreased need for inotropes after birth. Dexamethasone has been associated, in a recent meta-analysis, with a reduced risk of IVH compared with betamethasone (relative risk [RR] 0.44; 95% CI = 0.21–0.92) (Brownfoot et al. 2013). However, dexamethasone may increase the risk of periventricular leukomalacia (Baud et al. 1999) and it is, therefore, still unknown which steroid is better overall (Brownfoot et al. 2013). Many more infants are no longer ventilated for hyaline membrane disease but manage on the newer nasal continuous positive airway pressure or infant flow systems. Surfactant is sometimes given, following the so-called InSurE procedure, where the infant is intubated, given endotracheal surfactant and then extubated. Another, even less invasive method is minimally invasive surfactant therapy or less invasive surfactant administration where surfactant is administered using a Magill forceps and a thin orogastric tube without the use of premedication or intubation (Dargaville et al. 2013). Not having to be ventilated has led to less handling and the elimination of procedures during which fluctuations of cerebral blood flow will occur, such as endotracheal suctioning. When ventilation is required, more care is taken to avoid the infant fighting the ventilator and the use of muscle paralysis decreases the risk of IVH, but is not recommended (Cools and Offringa 2005). An increased risk of developing GMH-IVH using low-frequency oxygen ventilation (HFOV) has been suggested but, in a systematic review, this was found to be significant only in a subgroup of two trials not using a low-volume strategy with HFOV (Cools et al. 2009).

Delayed cord clamping has been shown to reduce the incidence of GMH-IVH. In a systematic review, there were no significant differences for infant deaths, but a significant difference in the incidence of GMH-IVH with less intraventricular haemorrhage (ultrasound diagnosis all grades) among 10 trials, enrolling 539 infants (RR = 0.59; 95% CI = 0.41–0.85) (Rabe et al. 2012). It was suggested that this could be the result of a higher flow in the superior vena cava after delayed cord clamping.

Pharmacological intervention may be promising, especially the prophylactic use of indomethacin, immediately after birth. The results of a meta-analysis, involving 19 trials and a total of 2872 infants, showed a significant reduction in the incidence of grade III and IV haemorrhages, with a pooled risk ratio (RR) of 0.66 and a 95% CI of 0.53–0.82 (Fowlie et al. 2010). The children of the original cohort studied by Ment et al. (1994a, 1994b) were reassessed at 8 years of age and no effect of indomethacin was seen on long-term outcome (Vohr et al. 2003). It was of interest, however, that male preterm infants randomly assigned to saline tended to have lower scores on the Peabody Picture Vocabulary Test—Revised than all of the other preterm groups. Using functional MRI to assess long-term influences of early indomethacin exposure on language processing, a significant treatment-by-sex effect was demonstrated in three brain regions: the left inferior parietal lobule, the left inferior frontal gyrus (Broca’s area) and the right dorsolateral prefrontal cortex (Ment et al. 2006). Another large trial (Schmidt et al. 2001) also could not show an improvement in survival without sensory impairment at 18 months, despite a reduction in the incidence of severe GMH-IVH. A meta-analysis of ibuprofen involving 27 studies did not show a reduction in the incidence of GMH-IVH in a subgroup of 571 infants, with a typical RR of 1.21 (95% CI = 0.74–1.98) (Ohlsson et al. 2013).

Phenobarbital was the first drug used postnatally in the prevention of GMH-IVH. The first studies were promising, but a meta-analysis of 12 trials could not show a reduction in the incidence or severity of GMH-IVH (RR = 0.91; 95% CI 0.77 to 1.08) (Smit et al. 2013).

Other drugs such as ethamsylate and vitamin E are considered to have a stabilising effect on the fragile vessels in the germinal matrix. Ethamsylate looked promising at first and some studies reported a decreased risk in the incidence of any grade of GMH-IVH, but a recent meta-analysis was unable to find a reduction in mortality or neurodevelopmental impairment in treated infants (Fish et al. 1990; Hunt and Hey 2010). The data for vitamin E are controversial.

The use of magnesium sulfate given prenatally has been studied extensively and the data obtained give different results (Weintraub et al. 2001; Mittendorf et al. 2002). A systematic review published in 2009, involving over 6000 infants, substantially reduced the risk of CP (RR = 0.68, 95% CI = 0.54–0.87). The number of women who needed to be treated to benefit one infant by avoiding CP is 63 (95% CI = 43–87) (Doyle et al. 2009). No reduction in the incidence of either a small or a large GMH-IVH was found in a large, randomised, multicentre study (Crowther et al. 2003). In a multicentre, randomised controlled trial, no significant reduction was found for the incidence of a large GMH-IVH (2.1% vs 3.2%; RR = 0.64; 95% CI = 0.38–1.06). Moderate or severe CP occurred significantly less frequently in the magnesium sulfate group compared with the control group (1.9% vs 3.5%; RR = 0.55; 95% CI = 0.32–0.95) (Rouse et al. 2008). Although the number of women who needed to be treated to avoid one case of CP is 63, the treatment appears to be cost-effective (Bickford et al. 2013).

### WHITE MATTER INJURY

The most common hypoxic–ischaemic lesion in the preterm infant is white matter injury, previously most often referred to as e-PVL (Fig. 2.9). This condition has also been reported by Miller et al. (2000) in term infants, and the more focal punctate white matter lesions are also commonly seen in term infants with congenital heart disease (Andropoulos et al. 2010). The term ‘periventricular leukomalacia’ was coined by Banker and Larroche in 1962, describing softening (malacia) of the white (leukos) matter. Most of the infants in this study were born at more than 28 weeks’ gestation and were several weeks’ old at the time of death. Anoxic events were recorded...
in all. Pathological examination was able to show bilateral, although not necessarily symmetrical, coagulation necrosis adjacent to the external angle of the lateral ventricles. In more recent years the classic pattern is less often recognised and in a study by Paneth et al. (1990) only three of 15 infants with white matter necrosis showed the classic changes of PVL. A distinction is nowadays made (Volpe 2008) between the more focal type of white matter damage – with cystic lesions limited to the regions of the trigone and occipital horns, involving the optic radiations, sometimes extending more anteriorly in the frontoparietal white matter – and the more diffuse type, which is now more commonly referred to as leukencephalopathy or periventricular white matter injury (WMI) rather than PVL (Leviton and Gilles 1984; Back 2006). Although evolution into cystic lesions, well visualised with cranial ultrasonography, is the hallmark of the focal type, more diffuse changes in signal intensity can be noted on MRI, a more appropriate technique to diagnose the more diffuse white matter disease (Counsell et al. 2003). Cystic PVL was diagnosed for the first time using cranial ultrasonography in 1982 (Hill et al. 1982). The lesions were haemorrhagic in older pathology studies, in about 25% of the infants (Levene et al. 1983). The incidence of c-PVL has decreased over the last decade (Hamrick et al. 2004; van Haastert et al. 2011) from 5% to 10% to <1% in some centres.

Neuroimaging Correlates

The initial changes seen with ultrasonography are areas of increased periventricular echogenicity (PVE), which is a very subjective finding (Fig. 2.10). Some researchers suggest assessing PVE by comparing it with the echogenicity of the choroid plexus. The duration of the PVEs should be taken into account, and the longer they exist the more likely they are to represent white matter injury (WMI). It may also help to look at the homogeneity of the PVE. When there is inhomogeneity (‘patchy’ PVE), it is more likely that one is dealing with WMI, and the patchy areas often correlate with punctate white matter lesions (PWMLs) on MRI (Sie et al. 2000b; Ramenghi et al. 2007; Kersbergen et al. 2014) (Fig. 2.11). The ultrasound grading system, according to de Vries et al. (1992a) classified WMI into four categories based mainly on the presence and extension of cystic lesions. Grade I can be further divided into two subgroups: (1) homogeneous and (2) inhomogeneous (patchy) PVE (Table 2.2). This classification is still useful although cystic WMI is nowadays much less prevalent. Grade I can be divided into two subgroups: (1) homogeneous and (2) inhomogeneous (patchy) PVE.

The increasing use of MRI in the preterm population has shown other potential signs of WMI, such as punctate lesions and diffuse excessive low-signal intensity (DEHSI) (Rutherford et al. 2010b). DEHSI, noted on T2-weighted spin-echo sequences around TEA in up to 70% of preterm infants, could be a correlate of early PVEs, although there is poor correlation between PVEs and contemporary signal intensity changes in the white matter (Maalouf et al. 2001; Debillon et al. 2003; Miller et al. 2003; Inder et al. 2003a; van Wezel-Meijler et al. 2011). Measurements of diffusion parameters (apparent diffusion coefficient [ADC], fractional anisotropy [FA], axial

<table>
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<tr>
<th>Table 2.2 Staging system for periventricular leukomalacia (PVL)</th>
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<tr>
<td>Description</td>
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<tr>
<td>Grade I: transient periventricular echodensities persisting for &gt;7 days</td>
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<tr>
<td>(a) homogeneous PVE</td>
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<tr>
<td>(b) inhomogeneous PVE</td>
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<tr>
<td>Grade II: PVE evolving into small localized fronto-parietal cystic lesions</td>
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<tr>
<td>Grade III: PVE evolving into extensive periventricular cystic lesions</td>
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<tr>
<td>Grade IV: densities extending into the deep white matter, evolving into extensive subcortical cysts</td>
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PVE, periventricular echogenicity; c-PVL, cystic PVL; SCL, subcortical leukomalacia.
diffusivity and radial diffusivity) suggest that these findings truly reflect alterations of the white matter (Counsell et al. 2003, 2006; Cheong et al. 2009; Liu et al. 2012; Bassi et al. 2011).

In a small number of infants, areas of PVE gradually evolve into localised or more extensive cysts (Fig. 2.12). The smaller and more localised the cysts, the longer it will take for the cysts to develop. Small cysts may easily remain undetected. More than 50% of the small cysts were first seen using weekly ultrasound examinations beyond day 28 (Pierrat et al. 2001; de Vries et al. 2004). In more than half the infants the small cysts had resolved by TEA, resulting in mild ventricular enlargement (ventriculomegaly, ex vacuo dilatation) in some, but not all, infants. With fewer ventilated infants and a very low turnover rate, most infants will be referred back to the local hospital before the development of the cysts and come back to the follow-up clinic at TEA or beyond. When ultrasound examinations are no longer performed in the local hospital, the cysts will remain undetected, which is probably the major reason for the poor reputation of cranial ultrasonography in predicting CP (de Vries et al. 2004). When cranial ultrasonography is routinely performed every week during admission, at discharge and again at TEA, the risk of missing periventricular cysts becomes negligible (van Haastert...
et al. 2011). To improve the surveillance of the children who are most at risk of developing cysts, diffusion-weighted MRI (DWI) has been shown to play a potential role. Inder et al. (1999b) were the first to show extensive changes on DWI that preceded cystic evolution. Few data are available because only very limited numbers of infants with PVE have been studied at an early stage of this severe disorder (Bozzao et al. 2003; Kidokoro et al. 2008; Fu et al. 2009). A new MRI based classification system has recently been reported (Martinez-Biarge M et al. 2016). The score illustrates that MRI findings should be scored taking the presumed time of injury, the severity of the preceding lesions seen with cUS and MRI and the presence of other signs indicative of previous injury into account. (Table 2.3).

Cysts, even when extensive, will resolve over weeks’ to a few months, and MRI plays a major role for assessing the extent of the white matter damage later in infancy. A rather classic picture with irregular dilatation of the lateral ventricles, a variable degree of white matter loss, sulci abutting the ventricular wall, a delay in myelination and periventricular gliosis can be recognised later in infancy (Byrne et al. 1990; Truwit et al. 1992). De Vries et al. (1993) found a good correlation between the severity of neonatal ultrasound abnormalities and gliotic changes on MRI performed in infancy (Fig. 2.13). Newer techniques, using diffusion tensor imaging (DTI) can perform diffusion tensor tractography (DTT), and thus map and quantify the pyramidal white matter tracts of preterm newborn infants (Miller et al. 2002; Berman et al. 2005; Partridge et al. 2005). Counsell et al. (2006) showed significantly increased radial diffusivity in the posterior limb of the internal capsule and the splenium of the corpus callosum, as well as significantly increased radial and axial diffusivity in the white matter of the centrum semiovale, and frontal, periventricular and occipital white matter. Kersbergen et al. (2016) performed tractography of the corticospinal tracts and segmentation of the thalami, shortly after birth and again at TEA in infants with extensive c-PVL and the comparison group, and they could identify damage to the corticospinal tracts (CST) on the early MRI; this was still present on the term scan, whereas the changes in thalamic volume developed in the weeks’ between the early and TEA MRI. This suggests a difference between acute and remote effects of the extensive injury caused by c-PVL to the white matter.

Pathogenesis of PVL

The pathogenesis of PVL is multifactorial and less well understood than that for GMH-IVH. The condition was initially considered to be caused by hypoperfusion of boundary zones in the white matter, but studies using continuous blood pressure measurements have so far been unable to identify hypotension as an independent risk factor for white matter injury (Trounce et al. 1988; Dammann et al. 2002; Logan et al. 2011). Severe hypocapnia, which causes a decrease in cerebral blood flow, has been identified as an independent risk factor for c-PVL in several studies (Okumura et al. 2001; Shankaran et al. 2006; Resch et al. 2012). Both cerebral blood flow and cerebral oxygen delivery were found to be significantly reduced in infants who went on to develop c-PVL (Pryds 1994). Using NIRS, Tsuji et al. (2000) confirmed dysfunction of cerebral autoregulation in 17 of 32 preterm infants; nine of these children developed severe intracranial lesions compared with only two of the 15 with intact autoregulation.

Several interesting studies have found an association of ascending intrauterine infection, production of inflammatory cytokines and WMI (Minagawa et al. 2002; Nelson et al. 2003; Hansen-Pupp et al. 2005; Leviton et al. 2011). Moreover, elevated blood concentrations of proinflammatory
Figure 2.13  Inversion recovery sequence and T2-weighted MRI in a preterm infant with extensive cystic periventricular leukomalacia grade III. (a) Extensive cysts are seen in the centrum semiovale at term equivalent age whereas (b, c) late MRI performed at 2 years shows angular ventricular dilatation, extensive periventricular gliosis and severe white matter loss.
cytokines in the first postnatal weeks' have been correlated with adverse neurodevelopmental outcomes in very preterm infants (O'Shea et al. 2012). Leviton et al. (2005) suggested that white matter damage results from the innate and adaptive immune systems reinforcing each other. The relationship between chorioamnionitis and CP has been evaluated in a meta-analysis; chorioamnionitis was found to be a risk factor for both CP (RR = 1.9; 95% CI = 1.5–2.5) and PVL (RR = 2.6; 95% CI = 1.7–3.9) (Wu and Colford 2000). Another more recent meta-analysis, including studies performed between 2000 and 2009, showed that both clinical chorioamnionitis (OR = 2.42; 95% CI = 1.52–3.84), and histological chorioamnionitis (OR = 1.83; 95% CI = 1.17–2.89) were risk factors for CP (Shattov et al. 2010). However, newer prospective studies, using magnetic resonance techniques, have not found a significant association between histological chorioamnionitis and WMI on MRI, or with abnormal metabolic or microstructural brain development (Chau et al. 2009). Whether this difference between previous and newer studies is the result of heterogeneity of the studies included in the meta-analyses, or of improved neonatal intensive care, is still unknown (Chau et al. 2014). Chau et al. (2009) did find an association between WMI seen on early MRI and postnatal hypotension requiring treatment, and with culture-positive postnatal infections.

Back and Rosenberg (2014) have defined the 'developmental window of vulnerability' as the period in human white matter development that precedes the onset of myelination (23–32 weeks'), when the risk of hypoxic–ischaemic or oxidative injury to the metabolically active pre-oligodendrocyte is highest. During the peak time when WMI occurs, the late oligodendrocyte progenitors are predominantly present. These pre-oligodendrocytes are very vulnerable not only to glutamate, but also to other chemical mediators such as cytokines, adenosine and several reactive oxygen species (Volpe et al. 2011; Back 2014). It is increasingly recognised that an additional contributing factor in preterm diffuse WMI is an aberrant response to this acute pre-oligodendrocyte death. The pre-oligodendrocytes are regenerated but the new ones do not mature properly into the myelinating cells required for normal growth of white matter. This abnormal process has been called 'cerebral dysmaturation disorder' (Back and Miller 2014).

Clinical Manifestations

Clinical signs are uncommon and may easily go unnoticed. Seizures may occur, but are often subtle or subclinical. Sequential abnormal findings on EEG during the neonatal period have been described in infants with WMI. Acute changes (decreased continuity, lower amplitude of background activity) are seen soon after birth, usually between days 1 and 4, whereas chronic changes (disorganised pattern with or without frontal and/or occipital sharp waves, positive rolandic sharp waves and abnormal brushes) are observed mainly between days 5 and 14. In cases of extensive c-PVL these EEG abnormalities are more severe and persist longer (Kidokoro et al. 2009). Positive rolandic sharp waves are specifically associated with WMI in preterm infants (Marret et al. 1992); one study showed a better sensitivity in preterm infants with a gestational age >28 weeks' (Baud et al. 1998). The frequency of these positive rolandic sharp waves in infants with WMI has been related to later neurodevelopmental outcomes (Vermeulen et al. 2003). Infants with milder degrees of WMI may not show positive rolandic sharp waves, and their frontal and occipital sharp waves may have higher sensitivity (Okumura et al. 2003). Lethargy or hypotonia may be present in the acute phase and some infants may be ventilator dependent, being acutely ill with septicaemia or necrotising enterocolitis. A characteristic picture is usually recognised after several weeks', when the infant becomes increasingly irritable and shows hypertonia, with extension of the lower limbs and flexion of the upper limbs. Tremors and startles are common and the Moro reflex is often abnormal. General movement studies reported a pattern of movements, called 'cramped—synchronised' (Cioni and Prechtl 1990), which has been associated with the site and extension of the white matter injury (Bos et al. 1998; Spittle et al. 2008). This abnormal pattern of general movements during the first 6 weeks' of post-term age predicts impaired motor development, especially when is followed by absent 'fidgety' movements at 3 months (Spittle et al. 2009). Cortical visual impairment is often recognised in infancy in these children (Lanzi et al. 1998; Fazzi et al. 2009). Although (subcortical) tracking can be elicited at TEA (Eken et al. 1994b; Cioni et al. 1997), more refined visual assessments in the neonatal period have shown abnormal visual function in a large proportion of infants with WMI (Ricci et al. 2011). Cortical visual impairment in children with WMI not only is the result of injury to the optic radiations and occipital cortex but is also related to thalamic atrophy which is so commonly seen in these infants (Ricci et al. 2006).

Neurodevelopmental Outcome

Neurodevelopmental outcome is invariably poor in infants with extensive cystic lesions in the parietal and occipital white matter, due to interruption of conduction in the fibres descending from the inner aspect and superior part of the hemisphere, which are involved in the motor function of the lower limbs and/or the optic radiation. This explains why they cause spastic diplegia and/or visual impairment. Advanced MRI techniques have shown that, in addition to the injury to the corticocospinal tract, children who develop spastic diplegia have reduced cortical volume and connectivity in the somatosensory and motor areas (Lee et al. 2011), as well as disruption of thalamocortical connections (Hoon et al. 2009). Cystic PVL is the most powerful predictor of later CP, usually spastic diplegia (van Haastert et al. 2011). Single cysts or cysts restricted to the frontoparietal, periventricular, white matter carry a better prognosis with a normal outcome or milder diplegia (Pieratt et al. 2001). Even PVE without cystic evolution carries a small risk of about 5–10% of developing CP, more often seen in the infants with longer
duration of the PVE (Chen et al. 2004; de Vries et al. 2004; Resch et al. 2006). Jongmans et al. (1993) showed that almost half the children with PVE who did not develop CP developed transient abnormalities in tone pattern, and were noted to have a higher total impairment score when assessed again at the age of 6 years with the Movement ABC test. The severity and extent of WMI predict not only the risk of CP, but also its severity and functional impact. The vast majority of infants with PVE without cystic evolution (PVL grade I) who develop CP have mild motor impairment and are able to walk independently before school age. PVL grade II is associated with a more significant motor impairment, but most of these children will still reach independent or assisted ambulation. In contrast, children with extensive PVL (grades III and IV) will show severe motor impairment (spastic diplegia or spastic quadriplegia) and will not walk or will require assistance to walk (Pierrat et al. 2001; Serdaroglu et al. 2004; van Haastert et al. 2008).

Cerebral visual impairment (CVI) caused by damage to the optic radiations, the occipital cortex and/or the visual association areas is highly prevalent in children with c-PVL. The range of visual problems is wide, from mild-to-moderate impairment (suboptimal visual acuity, restriction of the visual fields, visuospatial problems) to complete blindness (Dutton 2013). Abnormal signal intensity in the optic radiations, reduced volume in the periventricular white matter, atrophy of the calcarine cortex and reduced thalamic volume seen on MRI have been related to the presence and severity of visual impairment in these children (Ricci et al. 2006). Even in children with normal intelligence and normal visual acuity, impairment of higher visual abilities (visual object recognition, visuospatial skills, visual memory) is common (Fazzi et al. 2009). Strabismus and refractive errors are also frequent in children with c-PVL (Jacobson and Dutton 2000).

Cognitive impairment is the other main sequel of c-PVL. Performance scores are usually lower than verbal scores (which can be within the normal range), reflecting the impact of visuo perceptual impairments on learning abilities (Pagliano et al. 2007).

The effect of punctate white matter lesions and DEHSI on later outcome is still controversial. Punctate lesions did not have a negative influence on early neurodevelopmental outcome according to some authors (Cornette et al. 2002; Kersbergen et al. 2014), but others have shown an association between the presence of more than six of these lesions with lower developmental scores and a higher risk of CP (de Bruïne et al. 2011). Volume and location of PWML was quantified on MRI in 216 neonates (median gestational age 27.9 weeks) who had motor, cognitive, and language assessments at 18 months corrected age. PWML were present in about one third of the infants who were scanned at a median postmenstrual age of 32 weeks and were seen at 18 months corrected age. Infants with greater PWML volumes in frontal, parietal, and temporal lobes had adverse motor outcomes (all, p < 0.05), but only frontnal WMI volumes predicted adverse cognitive outcomes (p = 0.002) (Guo et al 2017). Some groups have found an adverse effect of DEHSI on learning abilities (Dyet et al. 2006; Parihk et al. 2013; Pogribna et al. 2014), whereas others have not found this association (Kidokoro et al. 2011; de Bruïne et al. 2011; Hart et al. 2011). An important observation by Inder et al. (1999a) was the loss of grey matter volume at TEA using three-dimensional volumetric MRI, following (non-cystic) white matter disease. A later study by the same group confirmed these findings in a larger cohort of preterm infants (Inder et al. 2005). Since then, several studies have described this secondary loss of grey matter volume in preterm infants, not only during the neonatal period, but also throughout childhood and adolescence. These findings have been correlated with lower developmental scores and suboptimal cognitive function (Boardman et al. 2010; de Kieviet et al. 2012).

**Prevention**

Very few data are available with regard to the prevention of WMI, but over the years a decrease in the prevalence has been noted in several units, and the extensive cystic form has become a rare disease (Hamrick et al. 2004; van Haastert et al. 2011). Improved obstetric and neonatal care appears to play an important role. In utero transfer, increased use of antibiotics in the management of prolonged rupture of membranes and the use of antenatal corticosteroids all appear to be protective (Kenyon et al. 2001; Roberts and Dalziel 2006). Although the first retrospectives studies observed a more neuroprotective effect of betamethasone compared with dexamethasone (Baud et al. 1999; Canterino et al. 2001), later prospective clinical trials have not found the same association and it is still unclear whether one steroid has advantages over the other (Brownfoot et al. 2013). The use of less aggressive ventilation strategies has proven to reduce the risk of hyperventilation and hypocarbia and has been associated with a decreased risk of preterm WMI (Peng et al. 2014). Elevated hypoxanthine in plasma and protein carbonyl levels, in the CSF of children who went on to develop c-PVL, suggested involvement of free radical damage (Russell et al. 1992; Inder et al. 2002). So far only one randomised study has been performed using allopurinol, showing no protective effect (Russell and Cooke 1995). Another potentially neuroprotective drug is human recombinant erythropoietin (EPO). EPO is routinely used in preterm infants to prevent and treat anaemia, but is also known to protect against glutamate toxicity, inhibit injury-induced apoptosis and attenuate nitric oxide release in the nervous system (Brown et al. 2009). A recent meta-analysis of seven clinical trials has shown that EPO is associated with a small but significant reduction in the rate of global neuro-developmental disability (RR = 0.77; 95% CI = 0.60–0.99), but not with a reduced rate of CI, or a lower rate of motor, cognitive or visual impairment (Zhang et al. 2014). It is not clear whether this improvement is the result of a reduction in the occurrence of WMI, because this outcome has not been specifically reported. A randomized, double-blind, placebo-controlled study was recently conducted in Switzerland between 2005 and 2012, enrolling 495 infants. In a nonrandomized
subset of 165 infants (n=77 erythropoietin; n=88 placebo), brain abnormalities were evaluated on MRI acquired at term-equivalent age. Infants treated with recombinant human erythropoietin (rhEPO) had less often abnormal scores for white matter injury (22% [17/77] vs 36% [32/88]; adjusted risk ratio [RR], 0.58; 95% CI, 0.35-0.96), and grey matter injury (7% [5/77] vs 19% [17/88]; adjusted RR, 0.34; 95% CI, 0.13-0.89) (Leuchter et al 2014). Neurodevelopmental outcome data was available for 365 (81%) of the 448 infants at a mean age of 23.6 months. In an intention-to-treat analysis, mean MDI was not statistically significantly different between the rhEPO group (93.5 [SD, 16.0] [95% CI, 91.2 to 95.8]) and the placebo group (94.5 [SD, 17.8] [95% CI, 90.8 to 98.5]) (Natalucci et al 2016). Apart from EPO other erythropoiesis-stimulating agents are being tested. Darbepoetin alfa is a synthetic form of EPO with an increased half-life. A recent randomised multicentre clinical trial comparing EPO, darbepoetin alfa and placebo has shown better cognitive outcomes and a reduced rate of CP at 18–22 months in infants treated with either EPO or darbepoetin (Ohls et al. 2014). Again the effect of treatment on the presence and extent of neonatal WM injury has not been reported. Other studies using different regimens of EPO within the first 4 postnatal weeks’ are now under way.

As with GMH-IVH, antenatal magnesium sulfate administered to women at risk of preterm delivery seems to be beneficial for reducing the incidence of c-PVL and the risk of later motor impairment (Doyle et al. 2009; Bickford et al. 2013).

**HYPOXIC–ISCHAEMIC ENCEPHALOPATHY**

Hypoxic–ischaemic encephalopathy (HIE) occurs in about 1–8 per 1000 livebirths worldwide (Lee et al. 2013) and is the most significant neurological problem in the neonatal period (Ferriero 2004; Volpe 2008). Although its incidence appears to have been declining recently in low-income countries, possibly as a result of improvements in obstetric care (Smith et al. 2000; Becher et al. 2007), HIE still carries a low burden in middle- and low-income countries, where more than 90% of HIE infants are born each year (Lee et al. 2013). It is a serious condition with 15–30% of affected infants dying during the immediate neonatal period and an additional 25–35% developing permanent neurological sequelae (Volpe 2008; Lee et al. 2013). Over the last three decades it has been emphasised that the role of perinatal hypoxia in the causation of cognitive impairment and CP was considerably overrated (Freeman and Nelson 1988; Bax and Nelson 1993, Nelson and Blair 2015). Badawi et al. (1998) found that many affected infants had been exposed to antenatal risk factors, such as maternal infertility treatment, or thyroid disease, whereas others had both ante- and intrapartum risk factors. However, the definition of encephalopathy used in that study was broad, and included infants who presented with seizures alone at any moment within the first week after birth and also a significant proportion of infants with genetic, congenital and developmental abnormalities. Other epidemiological studies, using more strict criteria for HIE, have shown that intrapartum events are the main or a significant contributing factor in the development of HIE (Ellis et al. 2000; Milsom et al. 2002; Martinez- Biarge et al. 2013). Although prenatal risk factors may be present and possibly make the infant more susceptible to intrapartum complications, Cowan et al. (2003) noted, in a prospective MRI study, that most of the 351 infants with neonatal encephalopathy had sustained brain injury at or near the time of birth.

As a result of the causal relationship between perinatal asphyxia and HIE not always being apparent, the non-committal term ‘neonatal encephalopathy’ has been proposed instead (Dammann et al. 2011; Leviton 2013). Although the diagnosis of HIE should not be made without a strict clinical evaluation, and alternative diagnoses such as infection, trauma, inborn errors of metabolism and other congenital disorders should be carefully considered, especially because they may have a significant impact on treatment, prognosis and genetic counselling, the term ‘neonatal hypoxic–ischaemic encephalopathy’ should be used in those infants who present with neonatal encephalopathy of early onset, preceded by signs of perinatal hypoxia–ischaemia (low Apgar scores, metabolic acidosis, need for resuscitation), and show neuroimaging features consistent with an acute hypoxic–ischaemic insult (Volpe 2012).

**Pathogenesis**

The deficit in oxygen supply that produces HIE can result from two mechanisms: hypoxaemia, i.e. a reduced supply of oxygen in blood, and ischaemia, i.e. a reduced perfusion of the brain (Fig. 2.14a) (Douglas-Escobar and Weiss 2015). In most patients both are caused by asphyxia, i.e. hypoxia associated with hypercapnia. Acidosis, which is usually present with hypoxia, is largely related to increased production of lactate via anaerobic glycolysis, a much less efficient process than oxidation through the tricarboxylate cycle (Krebs cycle) and mitochondrial electron transport system. Oxidation of each molecule of glucose metabolised under anaerobic conditions generates only two molecules of $AT$ = ATPP compared with 38 under aerobic conditions. Despite a considerable increase in the rate of glycolysis and an increase in cerebral blood flow caused by acidosis and hypercapnia, the energy needs of the brain may not be satisfied. The increased rate of glycolysis results in a decline in brain glucose levels. Ultimately, there is reduction in brain cell phosphocreatine and ATP as a consequence of the lack of oxygen, the final electron acceptor. Ischaemia has similar effects to asphyxia. Glycolysis is increased but the uptake of glucose is prevented by impairment of the blood supply, and hence the low-energy phosphates are depleted and lactate production rises.
Figure 2.14a  Excito-oxidative cascade of events that mediate hypoxic–ischaemic brain injury. Severe hypoxia impairs oxidative metabolism, leading to neuronal depolarization and ischaemia. Ischaemia reduces delivery of the glucose necessary for anaerobic metabolism, which powers neurotransmitter reuptake pumps on perisynaptic astrocytes. This leads to flooding of the synaptic cleft with glutamate and neuronal depolarization, which in turn triggers opening of N-methyl-d-aspartate (NMDA) receptor channels and other calcium channels, including acid-sensing ion channels, leading to excess calcium influx into neurons. Calcium flooding through NMDA channels activates the enzyme nitric oxide synthase (NOS), leading to low levels of the toxic free radical neurotransmitter nitric oxide (NO). This toxic free radical, along with additional oxygen free radicals generated by reoxygenation of mitochondria after a period of hypoxia, attacks enzymes associated with oxidative phosphorylation and electron transport. Calcium toxicity is also mediated by activation of other enzymes, including caspases, calpains, other proteases and lipases, that attack mitochondria and other cellular machinery. Signals released from damaged mitochondria lead to apoptosis or programmed cell death, as long as energy supplies persist, but exhaustion of energy supplies leads to necrosis, in which cellular membranes are destroyed. Lactic acid accumulates when oxidative phosphorylation within mitochondria is impaired, but its toxicity seems to be less important in the neonatal brain than in adult brains. Similarly, cerebral oedema occurs when pumps required for water homoeostasis are impaired by reduced energy supplies, as a result of damaged mitochondria. Oedema seems to be a sign of energy failure rather than a cause of damage on its own. This excito-oxidative cascade occurs over a period of days to weeks. EAAT, excitatory amino acid transporter; Gln, glutamine; Glu, glutamate; nNOS, neuronal NOS; VDCC, voltage-dependent calcium channels.

Apoptosis could play a more prominent role in the evolution of hypoxic–ischaemic injury in the neonatal brain compared with adults; it could be even more important than necrosis after injury (Blomgren et al. 2007; Johnston et al. 2011). During neonatal brain injury several pathways, including excitotoxicity, oxidative stress and inflammation, occur simultaneously and interact with each other; all contribute to accelerated cell death by means of apoptosis or necrosis, depending on the region of the brain affected and the severity of the insult (McLean and Ferriero 2004; Blomgren et al 2007). Acute HIE consists of two successive stages, the second one, in which definitive/permanent brain damage occurs, is delayed for several hours and is referred to as secondary energy failure. The mechanisms of cell damage and death with hypoxia or ischaemia are not simply the result of energy failure. When a critical level of energy deficit has been reached this energy failure secondarily triggers a cascade of deleterious events. Such events take place over several hours. Excessive membrane depolarisation and the release of excitatory amino acid neurotransmitters, especially glutamate, lead to calcium influx through N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA*) membrane
Figure 2.14b Downstream signaling pathways that mediate the apoptosis–necrosis continuum. Delayed cell death signaling pathways mediate the effects of hypoxia–ischaemia in the brain. The extrinsic pathway mirrors the cells’ external environment and begins when inflammatory cytokines (to the right of the figure at the cell surface) bind to and activate Fas-cell death receptors, whereas the intrinsic pathway is activated when signals released from within stressed mitochondria activate caspase- and non-caspase-mediated, cell-death pathways within the nucleus. These two pathways activate common signaling networks within the mitochondria and the nucleus. Mitochondria exposed to caspase-induced stress can release either cytochrome c through channels formed by the Bax and Bak proteins in the outer mitochondrial membrane (caspase-mediated cell death) or apoptosis-inducing factor (AIF), which directly activates DNA fragmentation (non-caspase pathway). Cytochrome c can combine with Apaf1 and caspase 9 to form the apoptosome, which triggers activation of caspase 3. DNA breaks mediated by free radicals such as NO· and peroxynitrite activate poly-ADP-ribose polymerase 1 (PARP1), which consumes NAD+ and worsens energy shortage for mitochondria (shown within the nucleus). Convergence of signalling for the extrinsic (Fas) and intrinsic cell-death pathways is responsible for the interaction between infection (endotoxin) and hypoxia–ischaemia that increases cell death. AIF, apoptosis-inducing factor; Apaf1, apoptotic protein-activating factor 1; Bax and Bak, proapoptotic proteins that form channels in outer mitochondrial membrane releasing cytochrome c to trigger apoptosis; BclXL, antiapoptotic proteins in the Bcl2 family of proteins; Bid, BH3 interacting domain proapoptotic protein; CAD, caspase-activating DNase; Cyt c, cytochrome c; FADD, Fas adaptor death domain protein; Fas, death receptor in tumour necrosis factor family; FASL, Fas death receptor ligand; GSH, glutathione, an antioxidant; IAP, inhibitor of apoptosis; NAD, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; SMAC, antagonist of inhibitor of apoptosis; tBid, truncated BH3-only proapoptotic protein; PAR, poly-ADP ribose formed by ribosylation of DNA and proteins; Vm, membrane potential; VSSC, voltage-sensitive calcium channel.

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receptors, and to the accumulation of cytosolic calcium (Robertson and Groenendaal 2012). Calcium, in turn, activates various lipases, proteases and nucleases with the resultant injury to essential cellular proteins. Activation of caspases, a family of proteases that are the primary mediators of apoptosis, results in proteolysis of cytoskeletal proteins and kinases, which eventually leads to nuclear fragmentation (Fatemi et al. 2009) (Fig. 2.14b). (Fig 2.16 and 2.17)

Another apoptotic pathway is mediated by free radicals, which are also generated as a direct or indirect result of increased cytosolic calcium. They play a role in peroxidation of fatty acids, membrane injury and cell necrosis. The developing brain is more vulnerable to oxidative stress because of two reasons: first because of its higher content in pro-oxidant substances such as polyunsaturated fatty acids and iron; and secondly because of the immaturity of its antioxidant defence system (Robertson and Groenendaal 2012).

The third main factor implicated in brain cell death is inflammation. Hypoxia–ischaemia induces an inflammatory response within minutes after the insult, which in turn exacerbates brain injury (Liu and McCullough 2013). Pre-existing fetal infection/inflammation may worsen hypoxic–ischaemic brain injury (Fatemi et al. 2009). The potential mechanisms include production and release of cytokines and microglia activation (Fatemi et al. 2009; Robertson and Groenendaal 2012; Liu and McCullough 2013).

**Neuropathology**

Early MRI studies revealed two main patterns of injury in neonates with HIE. Infants who had sustained acute, near-total, intrapartum asphyxia showed a consistent pattern of injury to the basal ganglia, thalami and brain stem, with relative sparing of the cortex and white matter (Barkovich 1992; Pasternak and Gorey 1998; Sie et al. 2000a) (Fig. 2.15). These lesions are bilateral and symmetrical, and found particularly in the ventrolateral thalami, posterolateral lentiform nuclei, posterior mesencephalon, hippocampi and sometimes the peri-rolandic cortex (Barkovich 1992). In contrast, in infants with partial, prolonged asphyxia, brain lesions are more diffuse, associated with oedema, and affect mainly the cortex and subcortical white matter in the vascular watershed zones (anterior–middle and posterior–middle cerebral arteries); they are often referred to as a boundary zone or watershed injury (Barkovich 1992; Miller et al. 2005). An overlap between the two main types of injury is, however, commonly seen (Figs. 2.16 and 2.17).

These patterns of injury seen on neonatal neuroimaging have been correlated with different perinatal antecedents and neonatal clinical courses. The basal ganglia–thalamus (BGT) pattern is typically seen in infants who have been exposed to a sentinel event during labour (uterine rupture, placental abruption, cord prolapse, tight nuchal cord) or to a prolonged terminal bradycardia. These infants are usually born in a poor condition, with a moderate-to-severe encephalopathy, a multisystem dysfunction that may be mild or absent and a motor outcome that is consistently impaired (Pasternak and Gorey 1998; Miller et al. 2005; Okerefor et al. 2008). Infants with the white matter/watershed pattern of injury are generally born in a better condition and experienced milder clinical courses, although they can experience hypoglycaemia and infection more frequently (Miller et al. 2005; Li et al. 2009; Harteman et al. 2013a; Wong et al. 2013). A recent study has found an association between this white matter/watershed pattern of injury and the presence of the MTHFR 677 CT or TT genotypes, and with higher levels of homocysteine (Harteman et al. 2013a). Motor outcome is normal in most of these children, but cognitive and behavioural problems are common (Steinman et al. 2009; van Kooij et al. 2010; Martinez-Biarge et al. 2012; Harteman et al. 2013b).

An association between these two different patterns of injury and placental pathology has recently been shown. The white matter/watershed pattern of injury, with or without concomitant BGT lesions was associated with fetal placental thrombosis and with decreased maturation of the terminal villi, whereas none of the placentas from infants with predominant BGT injury pattern showed evidence of decreased maturation.
This suggests a role for antenatal, chronic hypoxia in the white matter/watershed pattern of injury (Harteman et al. 2013c). (Fig 2.16 and 2.17)

**Clinical Manifestations**

The characteristic clinical signs of neonatal encephalopathy are an altered level of consciousness, abnormal muscle tone and motor responses, abnormal reflexes and abnormal cranial nerve function (especially feeding difficulties). Seizures are frequent (Volpe 2012). When the neonatal encephalopathy is due to an episode of perinatal asphyxia, this clinical syndrome is present from the time of birth, although its severity may change over the first few hours or days. The severity of the neonatal encephalopathy is commonly classified as stage 1, 2 or 3 according to the criteria by Sarnat, or alternately mild, moderate or severe, depending mainly on the degree of depression of consciousness. Although neonates with mild neonatal encephalopathy may be irritable or slightly lethargic, infants with moderate neonatal encephalopathy show different degrees of stupor and severely affected infants are usually comatose (Volpe 2008). The severity of encephalopathy correlates with the risk of mortality and overall adverse developmental outcome. Hypothermia treatment may alter the prognostic value of the clinical assessment in the first 6 hours after birth. Clinical trials on hypothermia have found that cooled infants might experience a faster clinical recovery and that persistence of severe encephalopathy at 72 hours increased the risk of death or disability, irrespective of the treatment (Shankaran et al. 2012a). Cooled infants
with moderate encephalopathy at 72 hours may have a better outcome than expected without hypothermia treatment (Gunn et al. 2008).

Seizures are common in the acute phase of HIE and affect 50–65% of infants with moderate-to-severe HIE (Gluckman et al. 2005; Azzopardi et al. 2009). A significant proportion of seizures is subclinical, especially after the administration of antiepileptic drugs, and whether to treat them remains controversial. Electrographic seizures have been associated with the severity of brain injury on MRI (Nash et al. 2011; Glass et al. 2011a; Shah et al. 2014), but there are insufficient data showing an association between these episodes and neurodevelopmental outcome. In a small randomised controlled trial treating only clinical seizures or clinical and subclinical seizures, there was a trend for a reduction in seizure duration when clinical and subclinical seizures were treated, and the severity of brain injury seen on MRI was associated with a longer duration of seizure patterns (van Rooij et al. 2010a). Recent observational studies suggest that hypothermia might reduce the number of electrographic seizures in infants with moderate and severe HIE (Low et al. 2012; Srinivasakumar et al. 2013).

Diagnosis of HIE

Diagnosis should be made based on a combination of the antecedents, clinical examination and clinical course, neuroimaging findings and electrophysiological data, and not just on the results of a single test. Clinical assessment of neurological status within the first 6 hours after birth is necessary to identify infants suitable for hypothermia treatment. Several scoring systems may help in the identification of infants with moderate or severe encephalopathy (Thompson et al. 1997). Subsequent neurological examinations during the first 3–4 days and at discharge provide useful prognostic information (Gunn et al. 2008; Murray et al. 2010; Shankaran et al. 2012a).

Amplitude-integrated EEG (aEEG) is one of the most useful tools in the clinical management of the infant with HIE and is also a good predictor of neurodevelopmental outcome. Interpretation of aEEG is based on the pattern recognition of background activity and voltage criteria. The combination of these two criteria produces five categories of aEEG traces in term infants: continuous normal voltage pattern, discontinuous normal voltage pattern, discontinuous background pattern burst suppression pattern, continuous background pattern of very low voltage and mainly inactive tracing (flat trace). There is a good correlation between these aEEG patterns and the EEG background pattern in term infants with moderate-to-severe neonatal encephalopathy (Toet and Lemmers 2009). The presence of an abnormal pattern (burst suppression, continuous low voltage or flat trace) within the first 6 hours after birth supports the diagnosis of significant (moderate or severe) HIE, and helps in the selection of infants for hypothermia treatment. The presence of abnormal aEEG patterns within the first 6 hours after birth, and the absence of recovery before 24 hours, both predicted death or significant disability before the introduction of therapeutic hypothermia (Toet et al. 1999; van Rooij et al. 2005). Onset of sleep–waking cycling before or after 36 hours of age also strongly correlated with outcome (Osrøedkar et al. 2005). Recent studies have shown that the predictive value of aEEG differs in cooled infants compared with non-cooled infants (Azzopardi 2014a). In cooled infants the predictive value of an abnormal aEEG trace within the first 6 hours is reduced. Infants treated with hypothermia may still have a favourable outcome even when an abnormal aEEG tracing persists beyond 24 hours, as long as the recovery occurs before 48 hours (Thoresen et al. 2010). The onset of sleep–wake cycling is also delayed in neonates treated with hypothermia (36 vs 24 hours), but most cooled infants will eventually show sleep–wake cycling within the first 4–5 days after birth (Thoresen et al. 2010; Takenouchi et al. 2011). The presence of an early normal or mildly abnormal EEG or aEEG pattern is highly predictive of a normal outcome, in both cooled and non-cooled neonates (Murray et al. 2009; Thoresen et al. 2010). The predictive value of the aEEG might be higher when it is combined with NIRS-monitored rScO₂ (Lemmers et al. 2013; Goeral et al. 2017).

Despite the widespread use of MRI techniques in the assessment of neonatal encephalopathy, cranial ultrasonography still plays an important role in the evaluation of brain injury (Daneman et al. 2006). Ultrasonography can detect abnormalities that suggest metabolic, congenital or infectious processes, such as established ventricular dilatation, germminolytic cysts, lenticulostriate vasculopathy, increased subarachnoid and interhemispheric space, cerebellar abnormalities, absent or abnormal corpus callosum and abnormal cortical folding (Leijser et al. 2007). When performed soon after birth, ultrasound examination can help to determine the timing of the injury. Established abnormal parenchymal echogenicity in the first 24–48 hours suggests a recent antenatal insult, whereas calcification or atrophy is a sign of a more longstanding injury (Leijser et al. 2006). Acute changes on an ultrasound scan typical of HIE have been well described and correlate well with contemporaneous MRI findings (Epelman et al. 2010). An early abnormal resistance index (≤0.55), measured by Doppler ultrasonography, predicts poor outcome in non-cooled infants (Eken et al. 1994a), but not in infants treated with hypothermia (Elstad et al. 2011), although it regains its predictive value after rewarming (Skranes et al. 2014). On conventional MRI, brain lesions are best seen during the second and third weeks after the hypoxic–ischaemic insult. BGT lesions (typically seen in the ventrolateral thalamus and the lentiform nuclei) are the most prevalent site of injury after acute perinatal hypoxia–ischaemia (Miller et al. 2005; Okereka et al. 2008), and are usually accompanied by abnormal signal intensity in the posterior limb of the internal capsule, which is a strong predictor.
The severity of the BGT injury, together with the signal intensity in the posterior limb of the internal capsule, is the best predictor of the presence and severity of motor impairment (Miller et al. 2005; Rutherford et al. 2010a; Martinez-Biarge et al. 2011). It is relatively common to see abnormal signal intensity in specific cortical regions, such as the central sulcus, the interhemispheric fissure and the insula. The adjacent white matter is also frequently affected. In severe cases, BGT injury may extend to the brain stem, a sign that has been associated with neonatal and later death (Martinez-Biarge et al. 2011). (Fig. 2.18)

Isolated white matter and cortical injury can be seen in neonates after a less severe perinatal course (Miller et al. 2005; Martinez-Biarge et al. 2012; Harteman et al. 2013b). White matter injury may also occur accompanying moderate or severe BGT injury either as part of the original insult or secondary to the BGT lesions, and is usually seen to evolve over the later neonatal period. In these patients repeat studies tend to show atrophy in the areas involved and gliotic changes can be seen later in infancy or childhood (Groenendaal and de Vries 2005). The predictive value of conventional MRI is not affected by the use of therapeutic hypothermia. Hypothermia treatment seems to reduce lesions in the basal ganglia and thalami, and in the white matter (Rutherford et al. 2010a; Cheong et al. 2012; Shankaran et al. 2012b).

Diffusion-weighted MRI within the first few days of birth can detect changes in the thalami, basal ganglia, hippocampus, brain stem and peri-rolandic cortex before conventional imaging, usually within the first 48–72 hours after birth (Rutherford et al. 2004), but visual assessment of diffusion changes may underestimate the severity of injury to these structures (Rutherford et al. 2010c). The apparent diffusion coefficient (ADC) can be calculated and may be of further use in making a distinction between those with milder or those with more severe injury to the basal ganglia (Rutherford et al. 2004; Barkovich et al. 2006); it may be of prognostic value (Hunt et al. 2004; Liuaw et al. 2009 Charon et al. 2016). Timing of the MRI during the first week after birth is crucial as areas of restricted diffusion may initially only involve the ventrolateral thalami, but will also show involvement of the basal ganglia a few days later (Barkovich et al. 2006). ADC values change over time and will pseudo-normalise by the end of the first week (McKinstry et al. 2002; Barkovich et al. 2006). They are low from days 1–2 to days 3–5, subsequently increasing thereafter (Barkovich et al. 2006). This pseudo-normalisation of diffusion imaging values could be delayed by 2–3 days in infants treated with therapeutic hypothermia (Bednarek et al. 2012). Diffusion changes can also be seen in the anterior and posterior watershed areas, usually in a bilateral and symmetrical distribution. The association between these white matter changes and later outcome is less obvious, and the outcome depends mainly on whether concomitant BGT injury is involved (Harteman et al. 2013b).

Prognosis and Outcome of HIE

Prognosis after HIE has traditionally been established based on the clinical severity of the encephalopathy, but this approach has some limitations, especially in children with moderate HIE, in whom prognosis has always been difficult to determine. Infants with mild encephalopathy have been
considered to have a good outcome, whereas those with severe HIE almost always die or develop significant neurodevelopmental sequelae. However, recent long-term follow-up studies have revealed that children with mild encephalopathy might be at increased risk of neurodevelopmental problems, including fine motor problems, specific neuropsychological deficits and behavioural difficulties (van Kooij et al. 2010; van Handel et al. 2010, 2012; Perez et al. 2013; Murray et al. 2016). The pattern and severity of the brain lesions have consistently correlated with the incidence and severity of the neurological sequelae. The recognition of these neuroimaging patterns may help to improve prediction of outcome.

Recent clinical trials on hypothermia have shown that the mortality rate in the neonatal period is around 20%–35% in infants with moderate-to-severe HIE; these figures are lower in cooled than in non-cooled neonates (Tagin et al. 2012). An additional 5–15% of these children will die over the next 18–24 months. Most neonatal deaths occur after redirection of care (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009; Jacobs et al. 2011; Glass et al. 2017). Infants with severe basal ganglia and brainstem injury seem to be at higher risk of post-neonatal death (Martinez-Biarge et al. 2011).

CP is the most severe sequela after neonatal HIE and affects 25–35% of survivors of moderate-to-severe HIE (Azzopardi et al. 2009; Jacobs et al. 2011). Although the clinical trials on hypothermia reported a slightly reduced risk of CP in cooled infants, most children with CP still had significant motor impairment (Gross Motor Function Classification System GMFCS levels III–V) and were non-ambulant (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009; Simbruner et al. 2010; Jacobs et al. 2011; Natarajan et al. 2014). However, a recent observational study on cooled infants has reported significant less severe motor impairment in the subgroup of children with CP than the figures reported in the clinical trials (Jary et al. 2015) CP is more common and severe among children with basal ganglia-thalamic injury; whereas in children with lesions restricted to the white matter the incidence is much lower (Miller et al. 2005; Martinez-Biarge et al. 2011, 2012). Children with BGT injury who do not develop CP are still at risk of having mild motor problems at school age (van Kooij et al. 2010).

Clinical trials on hypothermia have reported a 25–35% prevalence of developmental delays (Bayley II or Griffiths Developmental Scales scores <70) in children with moderate-to-severe HIE at 18–24 months (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009; Simbruner et al. 2010; Jacobs et al. 2011). Two clinical trials have reported childhood outcomes after therapeutic hypothermia. In one, the prevalence of an IQ less than 70 in survivors was 27% in cooled and 33% in non-cooled infants; this difference did not reach statistical significance. The percentage of children who died or had severe disability, CP or an IQ <55 was significantly lower in the cooled group (Shankaran et al. 2012c). In the TOBY trial, cooled participants assessed at age 6–7 years were significantly more likely to have a normal IQ (≥85; 52% vs 39%). Again, the rates of severe disability and CP were lower in the cooled group (Azzopardi et al. 2014b). Assessing the cognitive abilities of children with significant motor impairment may be challenging and many long-term studies have focused on children who do not have CP. In these children, the extent of the damage to the white matter has been correlated with cognitive function at age 2–4 years (Steinman et al. 2009; Martinez-Biarge et al. 2012). Van Kooij et al. (2010) found that at age 9–10 years, 25% of children with mild and moderate HIE, who had not developed CP, had an IQ <1 standard deviation (SD) and 7% were <2 SD. Although the mean IQ of the subgroup of children with mild HIE was within the normal range, it was significantly lower than in the normal comparison group. More than 80% of children with CP had an IQ <85 at this age. As well as global low or suboptimal IQ, specific neuropsychological deficits have been described in these children, including attention problems, executive dysfunction and memory impairment (Marlow et al. 2005; van Handel et al. 2012). There is also increasing concern about the impact of HIE on behavioural functioning in childhood and adolescence. Van Handel et al. (2010) found that children with mild and moderate HIE had a higher rate of social problems at age 9–10 years compared with controls; anxious/depressed behaviours and attention problems were also significantly more prevalent in children with moderate HIE.

Visual deficits affect 10–20% of infants with moderate-to-severe HIE (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009); they are more frequent in children with severe BGT lesions or very extensive white matter injury (Mercuri et al. 2004a; Martinez-Biarge et al. 2012). Hearing impairment after HIE is less common; the reported prevalence is around 5% of survivors (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009). Low gentamicin levels in the neonatal period may be a risk factor for permanent hearing loss in infants treated with therapeutic hypothermia (Smit et al. 2013).

The risk of epilepsy in infancy is not well known, but it is estimated at around 10–15% in the group of children with moderate-to-severe HIE (Gluckman et al. 2005; Azzopardi et al. 2009; Liu et al. 2017). Risk factors for the development of later epilepsy are the severity of neonatal encephalopathy, the presence and severity of neonatal seizures and the extent of brain injury on neonatal MRI (van Kooij et al. 2010; Glass et al. 2011b; McDonough et al. 2017).

**Treatment and Prevention of HIE**

After many years without proven treatments, whole body or selective head cooling is now the standard of care for term infants with HIE in low-income countries, and it is increasingly used in middle- and low-income countries, although in these settings its efficacy remains unclear (Pauliah et al. 2013). Recent meta-analyses have shown that, when combined
A phase II double-blinded, placebo-controlled trial studied 50 newborn infants randomized to receive EPO (1000 U/kg intravenously; n = 24) or placebo (n = 26) at 1, 2, 3, 5, and 7 days of age. All infants had moderate or severe encephalopathy and underwent hypothermia. Neonatal deaths did not significantly differ between EPO and placebo groups (8% vs 19%, P = 0.42). Brain MRI at a mean age of 5.1 days showed a lower global brain injury score in EPO-treated infants; treated infants also obtained better scores on the Alberta Infant Motor Scale at 12 months. (Wu et al 2016).

Topiramate is an anticonvulsant drug with multiple mechanisms of action, including anti-glutamatergic properties. Topiramate has been shown to be safe in neonates with HIE treated with hypothermia (Filippi et al 2010) and one clinical trial using topiramate showed the drug to be safe but did not show a reduction in mortality and severe neurological disability (Filippi et al 2017).

Xenon is a non-toxic anaesthetic gas with very few side effects; it is known to reduce neurotransmitter release to antagonise NMDA receptors. One recent clinical trial (Azzopardi et al 2016) did not find a significant difference in lactate to N-acetyl aspartate ratio in the thalamus, measured with MRS, or in fractional anisotropy in the posterior limb of the internal capsule, measured with MRI, between 46 infants who received hypothermia in combination with 30% inhaled xenon for 24 hours and 46 infants who received only hypothermia. At the time of writing another clinical trial is testing the effect of 50% inhaled xenon for 18 hours in combination with hypothermia (Dingley et al 2014 [ClinicalTrials.gov identifier: NCT01545271]).

Another potential neuroprotective agent is melatonin, which is well tolerated in the neonatal period and has antioxidative
and anti-inflammatory properties. A recent controlled pilot study has shown that early administration of melatonin, in addition to hypothermia, is feasible and could ameliorate brain injury (Aly et al. 2015).

HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN THE PRETERM INFANT

HIE has been described in preterm infants, usually after a placental abruption, maternal pre-eclampsia or abnormalities of the fetal heart rate, leading to an emergency Caesarean section (Salhab and Perlman 2005; Logitharajah et al. 2009), although its incidence in this group is not well known. Preterm infants with HIE seem to have a low incidence of severe basal ganglia and brainstem injury with relative sparing of the cortex (Barkovich and Sargent 1995; Logitharajah et al. 2009). MRI findings within the first 6 weeks' can be used to predict neurodevelopmental outcomes, applying the same principles as in term infants with HIE (Logitharajah et al. 2009).

FOCAL LESIONS (NEONATAL STROKE)

Neonatal stroke includes arterial ischaemic stroke (70%) and cerebral sinovenous thrombosis (30%). Arterial ischaemic stroke can be defined as a documented partial or complete occlusion of a vessel in relation to a focal brain lesion, or pattern of lesions that can be explained only by occlusion of a specific brain vessel; however, neonatal cerebral sinovenous thrombosis (SVT) is the presence of a thrombus in a cranial venous sinus, a large deep brain vein or a smaller cortical or deep vein, with partial or complete occlusion (Govaert et al. 2009).

ARTERIAL ISCHAEMIC STROKE

The prevalence of perinatal arterial ischaemic stroke (PAIS) is estimated to be between 1 in 2300 and 1 in 5000 live births (Lee et al. 2005a; Schulzke et al. 2005; Darmency-Stamboul et al. 2012). Neonatal stroke is the second most common cause of neonatal seizures (Tekgul et al. 2006; Garfinkle and Shevell 2011; Weeke et al. 2015).

Recent attempts to identify risk factors with the use of population-based studies have implicated both antepartum factors, such as primiparity, pre-eclampsia, infertility and intrapartum growth restriction (Lee et al. 2005a; Kirton et al. 2011; Harteman et al. 2012b Martinez-Biarge et al 2016), and intrapartum factors, such as prolonged rupture of membranes, maternal fever, presence of meconium, prolonged second stage of labour and abnormal fetal heart rate (Kirton et al. 2011; Harteman et al. 2012b). One recent study has identified maternal smoking during pregnancy as an independent risk factor for neonatal stroke (Darmency-Stamboul et al. 2012). Others have emphasised the association with coagulation abnormalities (decreased levels of protein C, protein S and antithrombin III, and elevated levels of homocysteine and Lp(a) lipoprotein, protein Z), as well as certain genetic mutations and polymorphisms (factor V Leiden G1691A, antiphospholipid antibodies, factor II G20210A and MTHFR C677T) (Günther et al. 2000; Kurnik et al. 2003; Curry et al. 2007; Simchen et al. 2009; Kenet et al. 2010). However, as a result of the very low recurrence rate of neonatal stroke (Golomb et al. 2001; Kurnik et al. 2003; Fullerton et al. 2007), thrombophilic factors are unlikely to play a substantial role in the pathogenesis of perinatal stroke (Curtis et al 2017). Male infants are overrepresented in almost all epidemiological studies (Golomb et al. 2009; Govaert et al. 2009; Darmency-Stamboul et al. 2012).

PAIS may also present in association with some neonatal conditions such as meningitis and hypoglycaemia (Fitzgerald and Golomb 2007; Harteman et al. 2012b; van der Aa et al. 2013a). Infants with congenital heart disease are at low risk of perinatal and postnatal brain injury. Perioperative stroke, sometimes after balloon atrial septostomy, is the most common brain lesion seen in this group of neonates (McQuillen et al. 2007).

The left hemisphere is more frequently involved than the right (Govaert et al 2009; Kirton et al. 2011; Harteman et al. 2012b). Middle cerebral artery infarction accounts for 80% of all instances of PAIS, whereas the posterior cerebral artery is involved in 8–15% of cases (Govaert et al. 2009; van der Aa et al. 2013a). The anterior cerebral artery is rarely affected, but this may reflect the silent nature of symptoms related to the involvement of this vessel. In addition to the better-known cortical infarcts, perforator strokes are also possible in the neonatal period. Risk factors appear to be very similar to those for main artery strokes (Ecury-Goosen et al. 2013).

Clinical Manifestations of Perinatal Arterial Ischaemic Stroke

Acute onset of seizures within the first 48 hours of birth is the most common presenting feature of perinatal arterial ischaemic stroke (PAIS) (Kurnik et al. 2003; Golomb et al. 2007b; Kirton et al. 2011). The convulsions are usually of the focal clonic variety, but multifocal tonic or subtle seizures may also be seen. Although many infants with these seizures have undergone a complicated labour and suboptimal Apgar scores, most infants appear healthy in the immediate newborn period and are sent to the postnatal ward with their mother (Martinez-Biarge et al. 2016). Many infants show no major clinical neurological abnormality between seizures, although neonatal stroke in infants with mild or moderate HIE has been reported (Ramaswamy et al. 2004; Harteman...
basal ganglia and posterior limb of the internal capsule). The latter method was reported to be strongly associated with early and school age motor outcome (Mercuri et al. 1999, 2004b; Cowan and de Vries 2005). DWI plays an important role in early detection and, along with T1- and T2-weighted changes, can help to define the timing of the infarction (Dudink et al. 2009). Restricted diffusion within the infarcted parenchyma results in increased signal intensity and decreased ADC values on DWI during the first week after birth (Dudink et al. 2009; van der Aa et al. 2013b). Lower ADC values have been seen in larger middle cerebral artery strokes compared with smaller infarcts (van der Aa et al. 2013b). Abnormal signal intensity on DWI in the descending corticospinal tracts, including the cerebral peduncles, has been reported to be a reliable predictor for the development of hemiplegia (de Vries et al. 2005; Kirton et al. 2007; Husson et al. 2010) (Figs. 2.19 and 2.20). This abnormal signal intensity has been shown to precede Wallerian degeneration (de Vries et al. 2005) and is therefore referred to as ‘pre-Wallerian degeneration’. Established Wallerian degeneration of the ipsilateral corticospinal tract and secondary reduction in thalamic size/volume can also be seen on conventional imaging after the first month (Dudink et al. 2009). Restricted diffusion within the infarcted parenchyma results in increased signal intensity and decreased ADC values on DWI during the first week after birth (Dudink et al. 2009; van der Aa et al. 2013b). Lower ADC values have been seen in larger middle cerebral artery strokes compared with smaller infarcts (van der Aa et al. 2013b). Abnormal signal intensity on DWI in the descending corticospinal tracts, including the cerebral peduncles, has been reported to be a reliable predictor for the development of hemiplegia (de Vries et al. 2005; Kirton et al. 2007; Husson et al. 2010) (Figs. 2.19 and 2.20). This abnormal signal intensity has been shown to precede Wallerian degeneration (de Vries et al. 2005) and is therefore referred to as ‘pre-Wallerian degeneration’. Established Wallerian degeneration of the ipsilateral corticospinal tract and secondary reduction in thalamic size/volume can also be seen on conventional imaging after the first month (Dudink et al. 2009). Additional MRI techniques, such as diffusion tensor imaging, have recently shown to be useful in predicting outcome (van der Aa et al. 2011, 2013c).

EEG reveals characteristic focal abnormalities in most patients (Mercuri et al. 1999; Selton et al. 2003; Low et al. 2014). These include ipsilateral suppression of the background activity, unilateral theta bursts with intermixed sharp or spike waves and disturbed sleep cycling over the infarcted side (although usually still present), and a characteristic pattern of seizures (focal sharp waves and spike–polyspike seizures at a frequency of 1–2Hz over the area of infarction) (Low et al. 2014). These abnormalities can be detected soon after birth and are often present shortly after the onset of seizures. EEG abnormalities are also seen in the contralateral hemisphere, which may be related to the involvement of the other corticospinal tract.

![Figure 2.19](image-url)

**Figure 2.19** Term infant with neonatal seizures related to ischaemic stroke. MRI scans at (a, b) in the first week and (c) at 3 months. (a) The inversion recovery image shows a wedge-shaped area of lower signal intensity of the posterior branch instead of trunk of the right middle cerebral artery and (b) bilateral smaller areas of increased signal in the periventricular white matter, confirmed by the apparent diffusion coefficient map. The area of cavitation at 3 months is smaller than expected on the basis of the neonatal diffusion-weighted imaging. The child developed a mild hemiplegia.

Diagnosis of PAIS

Although the diagnosis of PAIS can be made using cranial ultrasonography in most cases (Cowan et al. 2005; Abels et al. 2006), the area of infarction may remain undetected, especially when ultrasonography is restricted to the first days after birth, or when the infarction is small or located superficially in the parietal or occipital region (Golomb et al. 2003a). The increased use of MRI has facilitated early recognition of this type of injury (Cowan et al. 1994; de Vries et al. 2005; Dudink et al. 2009). On T2-weighted images the infarct can be seen from day 2 as increased signal intensity in the cortex and white matter, associated with loss of grey–white matter differentiation and poor delineation of the borders during the first few days. On T1-weighted images, the affected cortex is initially of low signal intensity, changing to a low-signal intensity (cortical highlighting) after day 6, whereas the adjacent white matter is of moderately low-signal intensity for the first 8–10 days. Signs of tissue loss, including focal atrophy and cystic evolution, can be seen from the start of the third week, and especially after the first month (Dudink et al. 2009). The area of infarction can be described by looking at either the branches that are affected (main branch, cortical branch, or one or more lenticulostriate branches of the middle cerebral artery) or the number of sites that are involved (hemisphere, basal ganglia and posterior limb of the internal capsule). The latter method was reported to be strongly associated with early and school age motor outcome (Mercuri et al. 1999, 2004b; Cowan and de Vries 2005). DWI plays an important role in early detection and, along with T1- and T2-weighted changes, can help to define the timing of the infarction (Dudink et al. 2009). Restricted diffusion within the infarcted parenchyma results in increased signal intensity and decreased ADC values on DWI during the first week after birth (Dudink et al. 2009; van der Aa et al. 2013b). Lower ADC values have been seen in larger middle cerebral artery strokes compared with smaller infarcts (van der Aa et al. 2013b). Abnormal signal intensity on DWI in the descending corticospinal tracts, including the cerebral peduncles, has been reported to be a reliable predictor for the development of hemiplegia (de Vries et al. 2005; Kirton et al. 2007; Husson et al. 2010) (Figs. 2.19 and 2.20). This abnormal signal intensity has been shown to precede Wallerian degeneration (de Vries et al. 2005) and is therefore referred to as ‘pre-Wallerian degeneration’. Established Wallerian degeneration of the ipsilateral corticospinal tract and secondary reduction in thalamic size/volume can also be seen on conventional imaging after the first month (Dudink et al. 2009). Additional MRI techniques, such as diffusion tensor imaging, have recently shown to be useful in predicting outcome (van der Aa et al. 2011, 2013c).
after birth, even before the onset of the clinical seizures (Walsh et al. 2011). Neonatal seizures can be difficult to recognise on the basis of clinical observation alone (Malone et al. 2009). Continuous EEG monitoring should therefore be started in all infants with a suspected neonatal stroke and should continue until the infant is seizure free for at least 24 hours (Shellhaas et al. 2011). EEG is useful for detection of ongoing seizure activity and to monitor response to therapy; and also aids in the prediction of outcome. Mercuri et al. (1999) found that an abnormal background pattern, even when recorded on only two channels, was the best predictor of adverse motor outcome. Although the criterion standard for neonatal brain monitoring is continuous multichannel EEG, aEEG can be used to document the overall patterns of background activity and to identify seizures of longer duration. Shorter and some focal seizures can be missed with the use of aEEG alone (Boylan et al. 2013). In infants with unilateral injury, two-channel recording can detect more seizure patterns on the affected side, and sometimes also a difference in background activity, compared with one-channel recording (van Rooij et al. 2010b; Boylan et al. 2013); it is therefore the aEEG modality of choice in these neonates (Boylan et al. 2013).

Other investigations can be helpful in order to exclude a specific cause for the stroke: thrombophilia screen, echocardiogram, assessment of vascular neck anatomy and Doppler ultrasonography of the umbilical or femoral vessels if or when catheters have been used.

**Prognosis and Outcome of PAIS**

Unilateral spastic CP (USCP) is the most important sequela and affects 25–40% of infants with unilateral arterial infarction (Boardman et al. 2005; Lee et al. 2005b; Husson et al. 2010, Chabrier et al. 2016). The upper limb is more affected than the lower limb and almost all children can walk (Golomb et al. 2003b). An additional 30% of children with unilateral ischaemic infarction may show minor signs of motor impairment at school age, such as asymmetry or poor motor competence (Mercuri et al. 2004b). Motor signs usually appear towards the end of the first year, but neurological assessment at the age of 3 months (including assessment of general movements) can be helpful in identifying infants who will develop USCP (Guzetta et al. 2003, 2010; van der Aa et al. 2011). Global and cognitive development are usually normal during the first 2–3 years, and most children have good cognitive results at early school age (Ricci et al. 2008), but long-term longitudinal follow-up of these children has revealed that a significant proportion of them may show emerging deficits in several cognitive domains as academic demands increase (Westmacott et al. 2009; van Buuren et al. 2013, Chabrier et al. 2016). Usually these deficits are in the mild range and most children are still able to attend mainstream school. Cognitive impairment is more common in children who develop USCP and epilepsy (Golomb et al. 2007a; Ballantyne et al. 2008; van Buuren et al. 2013 Chabrier et al. 2016). Specific neuropsychological deficits, such as poor visuomotor integration, impaired working memory and poor complex language skills have also been described (Westmacott et al. 2009; van Buuren et al. 2013; Reilly et al. 2013). Boys seem to be at higher risk of poor performance than girls (Westmacott et al. 2009).

Abnormalities in visual function are not common, but can be seen in some children with large infarcts who subsequently develop USCP, and in children with infarcts in the territory of the posterior cerebral artery (Mercuri et al. 2003; van der Aa et al. 2013a).

Children who had PAIS are at higher risk of developing seizures or even epilepsy in infancy and childhood. The incidence of this problem is unknown (Chabrier et al. 2016) and the reported rates are very variable (Golomb et al. 2007a; Ricci et al. 2008; Wanigasinghe et al. 2010, Fox et al 2016). In a prospective study 73% of children who had a neonatal stroke were seizure free at the age of 3 years; only half of those who had seizures eventually developed epilepsy (Wusthoff et al. 2011). Epilepsy is more common in children who also have USCP (Golomb et al. 2007a).

**Treatment and Prevention of PAIS**

Management of infants with PAIS includes general supportive care, correction of hypoglycaemia, antibiotics in cases of...
documented or suspected infection, and anticonvulsants. Anticoagulation therapy is not recommended, unless there is a documented ongoing cardioembolic source or in neonates with recurrent infarcts (Monagle et al. 2008). One study has suggested that hypothermia could be protective in neonates with arterial ischaemic infarction, by reducing the occurrence of acute seizures. In this study all the treated infants had presented with encephalopathy and had been cooled within the first 6 hours of birth (Harbert et al. 2011). The lack of obvious symptoms during the first hours after birth, when hypothermia is thought to be neuroprotective, is a potential limitation in the treatment of neonatal stroke. Some pharmacological agents are currently being tested and could be beneficial in the near future. One of these, rhEPO, has anti-inflammatory and anti-apoptotic properties and has been found to be safe in a study in neonates with stroke (Wagenaar et al. 2017).

**CEREBRAL SINOVENOUS THROMBOSIS**

The reported incidence of cerebral sinovenous thrombosis (CSVT) varies from < 1 to 12 per 100 000 live births (Berfelo et al. 2010; Yang et al. 2010). Although infrequent, CSVT in the neonatal period is associated with a mortality rate of 10–20% (usually due to the associated comorbidities), and with a low incidence of long-term neurological sequelae. As in arterial ischaemic infarction, male infants seem to be at higher risk of CSVT (Golomb et al. 2009; Tan et al. 2011).

Antecedent risk factors and clinical history are usually different from infants with HIE or arterial ischaemic stroke. A significant number of neonates with CSVT have other medical conditions at the time of diagnosis, such as congenital heart disease, meconium aspiration syndrome or sepsis/meningitis, or had been on extracorporeal membrane oxygenation (ECMO) (Wu et al. 2002). Maternal and intrapartum complications (pre-eclampsia, chorioamnionitis, complicated delivery, low Apgar scores) have also been described (Wu et al. 2002; Fitzgerald et al. 2006; Berfelo et al. 2010). The presence of multiple risk factors is not uncommon (Wu et al. 2002). Dehydration has been traditionally associated with CSVT (deVeber et al. 2001), although, in recent studies, its frequency has decreased (Berfelo et al. 2010).

Prothrombotic disorders have been reported in 20% of infants with CSVT (deVeber et al. 2001), but, as in arterial infarction, their role in the pathogenesis of CSVT remains unclear. It has also been proposed that occipital bone compression of the superior sagittal sinus, which is associated with supine head positioning, might play a role in the pathogenesis of CSVT in neonates (Tan et al. 2011).

The sagittal and the transverse sinuses are the most commonly involved (Fitzgerald et al. 2006; Teksam et al. 2008; Tan et al. 2011). More than half the neonates with CSVT show involvement of multiple sinuses. (Fitzgerald et al. 2006; Tan et al. 2011; Kersbergen et al. 2011). The vast majority of infants with symptomatic CSVT have concomitant brain lesions, generally correlated with the corresponding venous drainage territory (Teksam et al. 2008). The most common lesion is intraventricular haemorrhage, usually associated with thalamic haemorrhage (Kersbergen et al. 2011) (see Fig. 2.3). Other patterns of injury that have been described are occipital or parietal-occipital infarction, periventricular infarction and haemorrhagic lesions in the caudate nuclei (Wu et al. 2002; Kersbergen et al. 2011).

**Clinical Manifestations of CSVT**

As in arterial stroke, seizures are the most common presenting symptom, occurring in 50–70% of cases (Wu et al. 2002; Fitzgerald et al. 2006; Berfelo et al. 2010), but more subtle signs are also frequent, including lethargy, apnoea, irritability, abnormal muscle tone and a full fontanelle (deVeber et al. 2001; Wu et al. 2002; Fitzgerald et al. 2006; Berfelo et al. 2010). Infants on ECMO may not show clinical symptoms because they are paralysed, and a low index of suspicion is needed to establish the diagnosis in these neonates (Wu et al. 2002).

**Diagnosis of CSVT**

Cranial ultrasonography should be performed in all neonates with seizures, apnoeas or other neurological symptoms, and can detect intraventricular and thalamic haemorrhages, which are highly suggestive of CSVT in term infants (Wu et al. 2003; Kersbergen et al. 2011). Colour Doppler ultrasonography is very useful in the evaluation of normal cerebral venous sinuses (Miller et al. 2012), and can suggest CSVT by showing complete or partial absence of flow from an occlusive thrombus (Berfelo et al. 2010). When IVH or unilateral thalamic haemorrhage is seen on ultrasonography, early confirmation of diagnosis with MRI within the next 24–48 hours is indicated. MRI including MR venography (MRV) can show lack of flow in a sinus, and can also define the site of the venous occlusion; it is, therefore, required to confirm the diagnosis (Roach et al. 2008; Kersbergen et al. 2011). Follow-up MRI, 6–12 weeks’ later, is useful to document recanalisation of the affected sinus, which occurs in almost all cases within the first 3 months (Moharir et al. 2011), and to delineate the extent and severity of the parenchymal lesions.

**Prognosis and Outcome of CSVT**

Abnormal neurodevelopmental outcomes range between 40% and 80% (Fitzgerald et al. 2006; Kersbergen et al. 2009; Berfelo et al. 2010) and include motor problems, cognitive impairment, epilepsy, visual deficits and development of posthaemorrhagic hydrocephalus. The presence of associated
BILIRUBIN ENCEPHALOPATHY

The term ‘kernicterus’ was initially applied to the yellow staining of the basal nuclei found post mortem in deeply jaundiced infants who died with severe erythroblastosis fetalis. Later, it was also used to designate the clinical picture of choreoathetosis and hearing loss that followed severe haemolytic disease. More recently the term has been applied to similarly stained brains of infants who died without blood group incompatibility and had only modest rises of blood bilirubin. Some authors have suggested that such modest rises could be associated with impairment of cognitive or other neurological functions, although others did not find such a relationship. The term ‘bilirubin encephalopathy’ is now more often used than kernicterus for the neuropathological findings of bilirubin staining of brainstem and basal nuclei, and for the classic neurological picture, even though neuronal damage can be present without staining; conversely, bilirubin staining may be an agonal phenomenon unrelated to bilirubin toxicity (Ahdab-Barmada and Moossy 1984). Some investigators have proposed a stricter definition requiring both staining and neuronal damage (see Volpe 2017), whereas simple staining of nuclei without neuronal lesions in preterm infants, often associated with only moderate hyperbilirubinaemia, is considered to be a different phenomenon. Similarly, the term ‘chronic bilirubin encephalopathy’ will be used for all demonstrated or possible sequelae of bilirubin toxicity. An incidence of one in 44 000 live births was recently reported from a Canadian-based population, with a bilirubin serum level exceeding 425 µmol/L or 24.8 mg/dL (Sgro et al. 2012). In another population-based study an incidence of approximately one in 95 000 live births was found for acute bilirubin encephalopathy in Ireland and the UK, based on surveillance from May 2003 to May 2005. The lower incidence can be explained by the higher cut-off value of 515 µmol/L (Manning et al. 2007).

NEONATAL STROKE IN THE PRETERM INFANT

There are very few reports on the prevalence and clinical characteristics of neonatal ischaemic infarction in preterm infants. In a tertiary referral centre in the Netherlands perinatal stroke was diagnosed in seven per 1000 preterm infants admitted to the neonatal unit (Benders et al. 2007). This incidence is much higher than in term infants. Only 23% of these infants presented with seizures or apnoeas; an additional 13% had HIE. In the vast majority, the diagnosis was made by routine cranial ultrasound examination. As in term infants, the left middle cerebral artery was the most affected territory, but lenticulo-striate infarcts were relatively more common than in term infants, especially among the more immature group (Benders et al. 2007). Reported risk factors for neonatal stroke in this population are twin-to-twin transfusion syndrome, intrapartum abnormal fetal heart rate pattern and neonatal hypoglycaemia (Benders et al. 2007; Golomb et al. 2008; Ecury-Goossen et al. 2013).

The scarce follow-up data available suggest that preterm infants who have an arterial ischaemic stroke experience more neurodevelopmental problems and a higher rate of CP than term infants (Golomb et al. 2008; Benders et al. 2009).

CSVT has been considered rare in the preterm infant (Wu et al. 2002), but its incidence in this group may be underestimated because most infants are asymptomatic. Systematic serial cranial ultrasound examinations in a preterm population have shown an incidence of SVT of 4.4% (Raets et al. 2013). Extensive white matter injury is the predominant pattern of lesions in preterm infants with CSVT. Intraventricular haemorrhage (usually of late onset) and unilateral thalamic haemorrhage can also occur, although less common than in term infants (Kersbergen et al. 2011).

Treatment of CSVT

Treatment for CSVT has been traditionally limited to supportive measures (correction of dehydration, cardiorespiratory management, antibiotics for sepsis/meningitis and pharmacological treatment of seizures). Although anticoagulation therapy remains controversial, it is becoming increasingly used worldwide (Jordan et al. 2010). The aim of the therapy is to reduce the propagation of the thrombus, which occurs in about 25% of cases (Moharir et al. 2010). Anticoagulation therapy appears to be safe, even in the presence of thalamic haemorrhage (Kersbergen et al. 2009), and has been associated with a decreased risk of thrombosis propagation (Moharir et al. 2010), although its impact on neurodevelopmental outcome is not yet clear (Moharir et al. 2011). The American College of Chest Physicians has suggested treating neonates with CSVT and, if there is no significant intracranial haemorrhage, with unfractionated or low-molecular-weight heparin for a period of 6–12 weeks’ (Monagle et al. 2008). The European Paediatric Neurology Society has stated that, in the absence of any contraindication, anticoagulation may be considered individually during the acute phase of CSVT in neonates, for a period of 6–12 weeks’ (Lebas et al. 2012).
Pathology and Pathogenesis

In addition to the macroscopic staining of the globus pallidus, dentate nuclei, cerebellar vermis, hippocampus and medullary nuclei, yellow pigment may be present in the meninges and choroid plexus. Microscopically, spongy degeneration and gliosis are present in the stained areas and in zones that are not macroscopically involved, such as the cochlear nuclei and pathways. Pigment deposition is visible in neurons and glial cells. Neuronal necrosis generally involves the same structures as bilirubin staining, although some structures, (e.g. Purkinje cells), may be severely affected without significant staining.

The mechanism of kernicterus is unclear. The interrelationship of albumin, free and bound bilirubin, and kernicterus or bilirubin encephalopathy is shown schematically in Figure 2.21. Free bilirubin, i.e. the fraction of bilirubin not bound to albumin, crosses the blood–brain barrier and exhibits neurotoxicity. Bilirubin is undoubtedly toxic when it reaches neural tissue, perhaps by inhibiting phosphorylation and respiration in mitochondria (Perlman and Frank 1988). Normally, bilirubin is maintained within the vascular compartment where it is bound to albumin in an approximately equimolar concentration. The small unbound fraction may increase as a consequence of displacement from bilirubin-binding sites on albumin by exogenous agents, such as certain drugs, or endogenous substances such as fatty acids. Bound bilirubin may not be harmless and it can cross the blood–brain barrier, especially when the latter is damaged by factors such as hypercapnia or hyperosmolarity, although unbound bilirubin is the major offender (Volpe 2017). In haemolytic disease, the low amount of free bilirubin accounts for the occurrence of kernicterus, at levels beyond 340 µmol/L (20 mg/dL), although much higher levels are not necessarily noxious (Newman et al. 2006). Petersen et al. (2014) studied the role of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), in particular the UGT1A1*28 genotypes, in extreme hyperbilirubinaemia (>24.5 mg/dL). They did not find an association between the UGT1A1*28 allele and the risk for developing extreme hyperbilirubinaemia. Determination of the binding capacity of albumin has not proved helpful in practice, the more so because many factors that increase the risk of bilirubin encephalopathy do not produce detectable increases in free levels. Even though preterm infants with low albumin levels, acidosis, sepsis or peri-intraventricular haemorrhage (Govaert et al. 2003) are much more likely to develop kernicterus than those without such factors, it remains impossible to predict which infant will exhibit bilirubin toxicity. In the study by Govaert et al. (2003), five preterm infants of 25–29 weeks’ gestational age presented with total serum bilirubin (TSB) levels below commonly advised exchange transfusion thresholds. Mixed acidosis was present in three infants around the TSB peak. The bilirubin: albumin (B:A) molar ratio was >0.5 in all, in the absence of displacing drugs. All failed to pass bedside hearing screen tests and had severe hearing loss on auditory brain response testing. Four of the five infants presented with severe developmental delay as a result of dyskinetic CP and hearing loss. In a prospective, randomised controlled trial, 615 preterm infants of 32 weeks’ gestation or less were randomly assigned to treatment based either on the B:A ratio and TSB thresholds or on just the TSB thresholds, and outcome was assessed at age 2 years. The additional use of the B:A ratio in the management of hyperbilirubinaemia in preterm infants did not improve their neurodevelopmental outcome (Hulzebos et al. 2014).

Some evidence (Perlman and Frank 1988) suggests that bilirubin could enter the brain in a reversible manner and be responsible for a ‘subclinical neurotoxicity’ that could either be transient or evolve into definitive neuronal damage. This hypothesis is based mainly on alterations of auditory and visual evoked potentials with hyperbilirubinaemia. Evoked potentials may return to normal after an exchange transfusion (Deliac et al. 1990). If this hypothesis were to be confirmed, it would be possible to contemplate exchange transfusion on the basis of clinical and electrophysiological signs rather than solely on bilirubin levels (Perlman and Frank 1988), but the evidence is far from complete and the method difficult to use in practice. A similar attempt using MRI (Palmer and Smith 1990) remained inconclusive.

Clinical and Neuroimaging Manifestations

BILIRUBIN ENCEPHALOPATHY IN THE TERM INFANT

The classic picture of the term infant with typical kernicterus is not common in developed countries, although there appeared to be a slight increase after the changes to the guidelines in the 1990s which allowed higher bilirubin levels before initiating treatment (Ebbesen 2000). The increase in the number of cases of kernicterus was considered by Ebbesen to have been caused by, among other things, (1) a decreased awareness of the pathological signs, (2) a change in the assessment of the risk of bilirubin encephalopathy and (3) difficulty in estimating the degree of jaundice in certain groups of immigrants. Furthermore, immigration and intermarriage allowed the spread of glucose-6-phosphate dehydrogenase (G6PD) deficiency mutants to geographical areas distant from its place of origin and thus transformed severe neonatal jaundice associated with G6PD deficiency into a global problem.

The first neurological signs develop between age 48 hours and 4 days. The early phase presents with lethargy, hypotonia and poor suck. These changes are usually reversible with appropriate treatment. In the intermediate phase, moderate stupor, irritability and hypotension are seen. Fever, low-pitched cry, drowsiness and hypotonia may be present. Hypertonia is manifested by the backward arching of the neck (retrocolitis) and trunk (opisthotonos). Many believe that acute bilirubin encephalopathy that has advanced to this stage is irreversible, but recent evidence suggests that reversibility may be possible (Hansen et al. 2009). In the advanced phase, pronounced retrocolitis/opisthotonos, shrill cry, anorexia, apnoea, fever, deep stupor to coma and seizures may be seen, and the infants may die. Although rare, an apparently normal outcome has been described (Hansen et al. 2009). A scoring system (bilirubin-induced neurological dysfunction – BIND) has
[Figure 2.21] Schematic representation of the relationship between albumin, free and bound bilirubin, and kernicterus or bilirubin encephalopathy. [Modified from Hansen and Bratild (1986).]  
(*) May be due to drugs (e.g. sulfonamides), low albumin levels, and perhaps other factors such as acidosis: also observed in Crigler–Najjar syndrome (glucuronyl transferase deficiency). Except in the latter case is almost exclusively observed in preterm infants.  
(**) Generally due to Rh haemolytic disease or ABO incompatibility.  
(***) Intervention might be possible at this point to prevent neurological involvement.
been developed to follow the onset, severity and progression of acute bilirubin encephalopathy (Hansen 2011). In this scoring system, characteristics of mental state, muscle tone and cry are grouped into three levels of increasing abnormality: stage IA, minimal signs; stage IB, progressive but reversible with treatment; and stage II, advanced and largely irreversible, but may be significantly decreased by treatment. Characteristics for each category are given a weight of 1, 2 or 3 according to their severity and then summed up for an overall score. Greater risk is associated with higher numbers (0–9). A recent study performed in 220 (near) term infants with severe hyperbilirubinaemia showed that the BIND score can be used to evaluate the severity of acute bilirubin encephalopathy and predict residual neurologic and hearing dysfunction. The BIND score was obtained serially at 6- to 8-hour intervals and were correlated with TSB, neurological and auditory outcomes. All infants with a BIND scores of 7-9 either died or suffered residual neurological and auditory impairment. Fifteen (62.5%) of 24 cases with moderate encephalopathy (BIND 4-6), were normal at follow-up following intervention. Three of 73 infants with mild encephalopathy (BIND scores 1–3) but severe jaundice (TSB ranging 33.5–38 mg/dL; 573–650 µmol/L) had residual neurological and/or auditory impairment. A BIND score ≥4 had a specificity of 87.3% and a sensitivity of 97.4% for predicting poor neurological outcomes (El Houchi et al 2017). Deafness and choreoathetosis may appear later, even in the absence of neurological signs in the neonatal period.

Neuroimaging is not straightforward. Cranial ultrasonography may show increased echogenicity in the pallidum, but MRI is the imaging method of choice, even though abnormalities are not seen in all affected infants (Fig. 2.22) (Cece et al. 2013). In a study by Gkoltsiou et al. (2008), 11 infants were reported with total serum bilirubin levels of 235–583µmol/L in the preterm and 423–720µmol/L in the term infants. On the early MRI, the T1-weighted sequence tended to show increased signal intensity in the globus pallidus. On later MRI, the predominant abnormality was increased signal intensity on T2-weighted images with low signal intensity on T1-weighted images. Early scans did not reliably predict motor deficits although all children with CP had abnormal central grey matter on later scans. In the absence of MRI abnormalities at term equivalent age it was suggested that MRI be repeated at age 5 months. Low signal intensity in the globus pallidus on T1-weighted images may be normal in late preterm infants and can be difficult to distinguish from pathology that may also be caused by liver disease, prolonged parental nutrition and manganese exposure (Mirowitz et al. 1991). Abnormalities in the subthalamic nuclei were seen only at term but were associated with hearing loss even when the neonatal auditory brainstem response (ABR) was reported as normal, suggesting that careful observation of this region is important at this age. In a large study by Cece et al. (2013), MRI, including DWI, was performed in 30 infants with acute bilirubin encephalopathy. Neonatal imaging abnormalities were seen in 22 of 30 infants. Rather than a decrease in ADC values in the globus pallidum, a significant increase was noted. In another large study (Wang et al. 2008), including 24 term infants with bilirubin encephalopathy, ADC values were also noted to be increased but this did not reach statistical significance. Similar to the study by Cece et al. (2013), not all infants (19 of 24) had abnormalities on their MRI. They were also able to
perform proton MRS (1H-MRS) and found that the peak area ratios of NAA: choline and NAA: creatinine were significantly decreased ($P<0.05$) in the patients compared with the comparison group in the basal ganglia.

**Bilirubin Encephalopathy in the Preterm Infant**

Making the diagnosis of bilirubin encephalopathy is especially difficult in the preterm infant. Several studies have shown that bilirubin encephalopathy in the preterm infant may not be recognised during the neonatal period (Govaert et al. 2003; Okumura et al. 2009). In a report on eight preterm infants with a gestational age <34 weeks, no infant showed neurological symptoms characteristic of classic acute bilirubin encephalopathy (Okumura et al. 2009). Gestational age was <26 weeks in six of the eight infants. Peak serum bilirubin levels were >15mg/dL in only three infants. All patients developed extrapyramidal motor impairment, without apparent spasticity after discharge. Dystonic posture and abnormal muscle tone were first recognised within 6 months (corrected age) in all patients. MRI showed typical signal intensity changes in the globus pallidus on T2-weighted imaging at age 6–8 months, but no abnormalities were found on neonatal MRI.

**Clinical Outcome of Bilirubin Encephalopathy**

There is no single criterion to determine whether neurological or neurodevelopmental problems are due to hyperbilirubinaemia in children and adults. In his review, Shapiro (2010) uses combined information from history, physical (neurological) examination and laboratory studies. On examination, athetosis (slow writhing movements), dystonia (abnormal tone, fixed postures, co-contraction of agonist and antagonist muscles), variable hypo-/hypertonia, spasticity, ataxia, incoordination, impaired upgaze, staining or flaking of deciduous teeth (enamel hypoplasia), dysarthria, hearing impairment or difficulty localising sound may be found. Although their cognitive function is extremely difficult to assess due to their severe movement disorders and deafness, Shapiro considers it to be well within the normal range in most children. As localisation can be characterised as either auditory or motor predominant, a new classification was proposed (Table 2.4).

Vandborg et al. (2012) studied outcome in term and late preterm infants with severe and extreme neonatal hyperbilirubinaemia (total serum bilirubin level >25mg/dL) with no symptoms of intermediate or advanced bilirubin encephalopathy in the neonatal period, and compared these infants with a matched control group. They used the parent-completed Ages and Stages Questionnaire (ASQ) and found no evidence of developmental delay in children aged between 1 and 5 years compared with a matched control group.

Several authors have entertained the possibility that bilirubin toxicity in preterm infants may remain unapparent in the neonatal period, but could be responsible for delayed development, hearing problems, and motor or learning difficulties in childhood. Van de Bor et al. (1989) found a relationship between the occurrence of CP (of undescribed type), as well as of minor developmental anomalies, and hyperbilirubinaemia in the first few days of life. In this large study, each increase in bilirubin level by 50 $\mu$g/dL was associated with a small increase in the frequency of neurological sequelae. Similar conclusions were drawn from a large cohort of 2575 infants, born in 12 centres in the USA between 1 January 1994 and 31 December 1997 (Oh et al. 2003). A significant association was found between peak total serum bilirubin (in mg/dL) and death or neurodevelopmental impairment (OR = 1.068; 95% CI = 1.03–1.11), Psychomotor Developmental Index <70 (OR = 1.057; 95% CI = 1.00–1.12) and hearing impairment requiring hearing aids (OR = 1.138; 95% CI = 1.00–1.30). Other large studies (Seidman et al. 1991; O’Shea et al. 1992) did not confirm a relationship between neonatal bilirubin concentrations and developmental problems or intelligence. A relationship with hearing loss seems to be better established (Govaert et al. 2003).

**Therapy of Bilirubin Encephalopathy**

The treatment of kernicterus in term infants with haemolysis rests on the prevention of excessive hyperbilirubinaemia.
Exchange transfusion is indicated for infants with erythroblastosis at a level of 340µmol/L (20mg/dL) (Hansen 2011). Prevention and prenatal treatment of blood group incompatibility have resulted in almost complete disappearance of this problem. In a study by Watchko and Claassen (1994) only three of 81 infants had demonstrated kernicterus at relatively low bilirubin levels. Half the remaining 78 infants had bilirubin levels in excess of those recommended by the US National Institute of Child Health and Human Development, so the indications for exchange remain uncertain (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia 2004; Wennberg et al. 2006). In preterm infants, exchange transfusion is of uncertain value and there is no agreement as to the levels at which it should be performed (Watchko and Maisels 2003). Although relatively safe, the procedure carries certain risks. Phototherapy effectively increases the removal process of bilirubin in preterm infants. The technique is safe, and breakdown products do not seem to produce bilirubin encephalopathy while lowering peak levels of bilirubin by an average of 70µmol/L (4mg/dL). The value of mesoporphyrin mesoporphyrin compounds inhibiting heme-oxygenase of bilirubin production is being tested and encouraging results have been reported, for instance in infants with G6PD deficiency (Kappas et al. 2001).

Low levels of bilirubin may induce some behavioural changes in the absence of encephalopathy but these are probably of limited significance.

### METABOLIC INSULTS: NEONATAL ASPECTS

Metabolic disorders are considered in Chapter 9. Only the specific aspects of metabolic problems in the newborn infant are discussed here.

#### NEONATAL HYPOGLYCAEMIA

The level of blood glucose concentration that leads to cerebral injury in newborn infants and adverse neurodevelopmental outcome is unknown: low blood glucose levels are observed during postnatal adaptation of healthy term infants without apparent adverse consequences, and the capacity to mobilise and use alternative cerebral fuels when blood glucose levels are low varies between patient groups. There is a lot of discussion about the definition of hypoglycaemia and the cut-off value of safe glucose levels in the newborn infant (Cornblath et al. 2000). The conventional definition of significant hypoglycaemia in the neonate is a blood sugar level of <1.1mmol/L (20mg/dL). Related to a paper by Koh et al. (1988), values <2.6mmol/L (45mg/dL) are now also considered to be potentially deleterious to the developing brain. Both figures are rather arbitrary because some infants may be symptomatic with levels of 1.6–2.2mmol/L (30–40mg/dL), whereas many others do not have symptoms even at levels well below 1.1mmol/dL. Other factors such as the rate of fall of glucose and the duration of low glucose levels and associated hypoxia–ischaemia are thus important. Asymptomatic, transient hypoglycaemia can be detected in 11% of all newborn infants during the first hours postpartum before oral feeding is initiated (Fenichel 1997), especially in those with fetal growth restriction or birth asphyxia, or in those born to mothers with diabetes or toxemia (Cornblath and Schwartz 1991). The incidence of symptomatic hypoglycaemia is certainly much lower. It is important to sample whole blood because the glucose concentration of plasma is higher than that of whole blood, and it is essential that accurate methods of measurement be used to make the diagnosis of neonatal hypoglycaemia, and to be aware that measurements from glucose reagent strips are not reliable in this low range (Beardsall 2010, Martinelli et al 2017).

#### Mechanisms and Pathology

The mechanisms of neonatal hypoglycaemia are diverse. Rarely infants suffer from grave conditions such as nesidioblastosis. In most, especially in small-for-gestational age neonates, an imbalance between a relatively large brain, which consumes glucose as its primary fuel, and a small liver depleted of glycogen reserves seems to compromise supply of glucose to the CNS. The absence of symptoms in many infants with hypoglycaemia may be related to the fact that the newborn brain can oxidise fuels other than glucose, such as ketone bodies, lactic acid and fatty acids.

The pathology of hypoglycaemia is reminiscent of that of hypoxia, with which it is often associated. Neuronal cell loss involves not only the brain but also the anterior horn cells of the spinal cord, but it usually predominates in the posterior part of the cerebrum.

In infants with neonatal encephalopathy after perinatal hypoxia–ischaemia, involvement of the white matter and the WS pattern of injury was associated with hypoglycaemia, and hypoglycaemia was also identified as an independent risk factor in the preterm (Benders et al. 2007) and term newborn infants with PAIS (Harteman et al. 2012b, 2013).

#### Neuroimaging Findings

As the posterior part of the cerebrum is not well visualised using the anterior fontanelle, in recent years information about brain injury has become available with the increased use of MRI. MRI data have shown predominant involvement of the parieto-occipital white matter, as well as abnormal signals in the deep grey matter structures of the thalamus and basal ganglia, after symptomatic neonatal hypoglycaemia in term neonates (Barkovich et al. 1998; Filan et al. 2006; Tarn...
et al. 2008; Burns et al. 2008). In the study of Tam et al. (2008) MRI was performed early, concentrating on DWI findings, whereas, in the study of Burns et al. (2008), neuroimaging was performed within the first 6 weeks after birth. In the study by Tam et al. (2008) there was a significantly higher incidence of occipital lobe findings. In a large study of more than 100 infants with hypoglycaemia, including also preterm infants and infants older than 28 days, abnormal MRI findings were found in 4% of preterm infants, 32.5% of term infants and 43.5% of older infants (Caksen et al. 2011). Abnormal MRI findings were significantly more common in symptomatic infants than in asymptomatic infants (Fig. 2.23).

Clinical Features of Neonatal Hypoglycaemia

Neurological manifestations of neonatal hypoglycaemia include apnoea, jitteriness, low-pitched cry, cyanosis, vomiting, seizures and coma, isolated or in any combination. The occurrence of symptoms seems to depend more on the duration of hypoglycaemia than on its degree. Several types can be observed. In the first few hours after birth, an ‘adaptive’ hypoglycaemia frequently occurs in infants of diabetic mothers, those with erythroblastosis fetalis and many preterm asphyxiated infants. Most infants with onset in the first 12 hours after birth remain asymptomatic. Secondary hypoglycaemia usually occurs in the latter part of the first day after birth and is seen in severely asphyxiated infants born at or before term. The part played by hypoglycaemia in such cases is difficult to disentangle from that of the primary disorder. The classic type is seen primarily in small-for-gestational age infants. Symptoms are present in about 20% of such patients. They appear in the latter part of the first day or in the second day.

The outlook depends on the severity and duration of the hypoglycaemia and on therapy. Recurrent hypoglycaemia, however, is usually associated with hyperinsulinism, glyco- genoses, fructose intolerance, or other disorders of carbohydrate metabolism or regulation. Congenital hypopituitarism, although infrequent, is an important cause because recognition is essential to avoid recurrences and intellectual disabilities. Symptomatic hypoglycaemia in otherwise healthy, breastfed, term newborn infants has also been reported and is seen in children where the breast milk intake is insufficient and additional intake not given (Moore and Perlman 1999). Breastfed children are known to have lower blood glucose concentrations and higher ketone body concentrations on days 2 and 3 after birth than formula-fed infants (Hawdon et al. 1994).

There is increasing evidence of neurodevelopmental sequelae after symptomatic neonatal hypoglycaemia, usually not in the form of severe CP but with some milder motor problems, visual, learning and behavioural difficulties, poor head growth and later seizures (Yalnizoglu et al. 2007; Caksen et al. 2011; Karimzadeh et al. 2011; Tam et al. 2012). Lasting effects may follow relatively mild hypoglycaemia. Koh et al. (1988) reported delayed nerve conduction velocities in children with marginal hypoglycaemia that persisted after correction of the metabolic defect. Lucas et al. (1988) found that children who had prolonged biochemical hypoglycaemia had a 3–14-point disadvantage on the Bayley scale compared with normoglycaemic children, although this was a retrospective study with consequent limitations. In a large study of almost 1000 moderately preterm infants (gestational age 32–36 weeks), hypoglycaemia, defined as at least 1 plasma glucose value <1.7mmol/L (30mg/dL) within the first 72 hours after birth, was noted in 8.1% of the infants. In the multivariable
analysis only hypoglycaemia remained significantly associated with a developmental delay (OR = 2.19; 95% CI = 1.08–4.46) (Kerstjens et al. 2012).

**Treatment of Neonatal Hypoglycaemia**

An algorithm for the management of severe hypoglycaemia was suggested by Boardman et al. (2013). Treatment of neonatal hypoglycaemia consists of the intravenous administration of 0.5–1.0g/kg of glucose as a 25% solution at a rate of 1mL/min, followed by continuous infusion of 8–10mg/kg per min. The bolus injection should be used only in case of emergency and should always be associated with an increase in the glucose intake after the bolus (AAP guidelines 2011). The underlying cause must be determined. Asymptomatic infants should probably have their glycaemia corrected by continuous infusion when blood glucose is <2.2mmol/L (40mg/L) (Deshpande and Ward Platt 2005).

**HYPOGLYCORRHACHIA WITHOUT HYPOGLYCAEMIA**

Hypoglycorrhachia without hypoglycaemia (De Vivo et al. 1991; Leen et al. 2010) is a rare condition, the importance of which lies in the possibility of active treatment and its diagnostic difficulties. The disorder is caused by deficiency of the carrier protein glucose transporter-1 (GLUT-1) that transports glucose from blood to the CSF. GLUT-1 deficiency syndrome is caused by mutations in the SLC2A1 gene in most patients, and results in impaired glucose transport into the brain (Leen et al. 2010). It is transmitted as an autosomal recessive trait and usually manifests clinically from the end of the first month onwards. GLUT-1 deficiency syndrome is caused by haploinsufficiency of the blood–brain barrier hexose carrier. Truly neonatal cases are known (Brockmann et al. 2001). The major clinical features are seizures, although ataxia, paroxysmal disturbances of consciousness and even periodic weakness have been observed. A low CSF lactate level may be a clue and the diagnosis is further supported with paired blood and CSF glucose samples. Treatment by ketogenic diet prevents neurological deficit and has been successfully maintained for several years.

**HYPERGLYCAEMIA**

Marked hyperglycaemia occurs occasionally in neonates with CNS disturbances (Cornblath and Schwartz 1991) and has a grave prognostic significance. Hyperglycaemia may be due to transient neonatal diabetes mellitus. This is a rare form of diabetes that presents within the first 6 months of life. In almost 70% of the cases the condition is due to genetic or epigenetic aberrations at an imprinted locus on chromosome 6q24, and can be sporadic or inherited. Most infants recover by 3 months of age but are predisposed to developing type 2 diabetes in later life (Temple and Shield 2010).

With increased survival of extremely preterm infants, hyperglycaemia is now also more commonly seen in the neonatal intensive care unit. In these very immature infants, hyperglycaemia is likely to be caused by altered metabolism, as well as the need for continuous parenteral nutrition. Hyperglycaemia in extremely preterm infants has been associated with increased rates of death, IVH, sepsis and retinopathy of prematurity, and with increased lengths of hospital stay. Alexandrou et al. (2010) have shown that hyperglycaemia, defined as a plasma glucose level >8.3mmol/l, occurring on the first day after birth, was associated with an increased risk of death and white matter reduction on the MRI performed at TEA. In term infants with perinatal asphyxia, hyperglycaemia occurring on day 1 was associated with death or worse gross motor outcome (Spies et al. 2014).

**DISTURBANCES OF ELECTROLYTE METABOLISM**

**Hypocalcaemia, Hypophosphatasia, and Hypomagnesaemia**

Hypocalcaemia is defined as a blood calcium level <1.75mmol/L (7mg/dL) and is often associated with hypomagnesaemia, a magnesium level <0.6mmol/L (1.5mg/dL). Two distinct forms of neonatal hypocalcaemia form the bulk of the patients seen in the neonatal period, but both have become very rare with improved neonatal care, total parenteral nutrition in the preterm infant and improved cows’ milk formulae.

Early hypocalcaemia occurs before 48 hours of age mainly in preterm infants, infants of mothers who are diabetic, and those who are small for gestational age or have suffered asphyxia. Between 21% and 60% of such infants have calcium levels <1.75mmol/L (7mg/dL) or ionised calcium levels <0.75–0.85mmol/L (3–3.5mg/dL). This form has no symptoms of its own, and any clinical manifestation observed is likely to be caused by the primary condition of the infant.

Late hypocalcaemia presents at between 5 and 10 days of life, typically in infants fed cows’ milk formulae with a low phosphorus content. The excess phosphate load cannot be completely excreted by the immature kidney and the resulting hyperphosphataemia induces hypocalcaemia. Infants born in winter or early spring to mothers of low social class with subclinical vitamin D intake are at particular risk. Late hypocalcaemia has become rare since modified formulae have been in common use.

The clinical features are those of classic ‘neonatal tetany’. The Chvostek and Trouseau signs can be elicited in infants with severe hypocalcaemia. Focal or multifocal clonic seizures appear in apparently normally alert and hungry infants. Jitteriness is almost universally present between seizures that occur repeatedly, and may last intermittently for several days if untreated. The prognosis for late hypocalcaemia is good. Remarkably, the seizures, even when lasting for hours and days, do not leave residua (Lombroso 1996).
Late hypocalcaemia may also occur in infants born to mothers with hyperparathyroidism. As maternal hyperparathyroidism is often clinically silent, routine determination of calcium and phosphorus in maternal blood is in order if no obvious cause for the hypocalcaemia is present. Hypocalcaemia is also a manifestation of Di George syndrome, in which the seizures may precede the signs of immunodeficiency that occur in association with cardiac and other malformations.

Another cause for hypocalcaemia may be the HDR syndrome, an autosomal dominant disorder characterised by hypoparathyroidism, sensorineural deafness and renal anomaly, caused by mutation of the GATA3 gene located at chromosome 10p15 (Ohta et al. 2011).

Hypophosphatasia (HPP) is a rare metabolic bone disease caused by loss-of-function mutations in the gene ALPL encoding the tissue nonspecific alkaline phosphatase (TNSALP). Infants may present with neonatal seizures and develop multicystic encephalomalacia. Enzyme replacement therapy has been reported (Whyte et al. 2012, Okazaki et al 2016).

Familial hypomagnesaemia with secondary hypocalcaemia (OMIM 602014) is an autosomal recessive disease that results in electrolyte abnormalities shortly after birth. Affected individuals show severe hypomagnesaemia (<0.08 mmol/L, 0.2 mg/dL) and moderate hypocalcaemia, which lead to seizures and tetany. The disorder was thought to be caused by a defect in the intestinal absorption of magnesium, rather than by abnormal renal loss of magnesium. Restoring the concentrations of serum magnesium to normal values by low-dose magnesium supplementation can overcome the apparent defect in magnesium absorption and in serum concentrations of calcium. Life-long magnesium supplementation is required to overcome the defect in magnesium handling by these individuals. This condition is due to a mutation of TRPM6 (Wälde et al. 2002).

**Hypercalcaemia and Hypermagnesaemia**

Hypercalcaemia in newborn infants may occur with fat necrosis in some infants receiving intravenous infusion of calcium gluconate, and in rare patients with a defect of intestinal transport of tryptophan, the so-called ‘blue diaper syndrome’. It is also a feature of Williams (‘elfin face’) syndrome, although it often goes unrecognised during the neonatal period (see Chapter 5). Prolonged moderate hypothermia is also an actual risk factor for subcutaneous fat necrosis and was seen several days after rewarming in 12 of 1239 infants registered with a national registry of newborn infants who were treated with moderate whole-body hypothermia (Strohm et al. 2011).

Neonatal hyperparathyroidism is a rare, severe condition that features hypotonia, failure to thrive, respiratory distress associated with multiple rib fractures and early death when untreated (Waller et al. 2004). Familial hypocalciuric hypercalcaemia (FHH) is an autosomal dominant condition caused by heterozygous loss of function of calcium-sensing receptor (CaSR) mutations (Hendy et al. 2000). However, individuals who are homozygous for CaSR mutations have neonatal severe hyperparathyroidism (NSHPT), which, unlike the relatively benign and asymptomatic FHH, can be fatal without parathyroideectomy (Waller et al. 2004). Hypercalcaemia may also be a feature of the more benign, asymptomatic, neonatal familial hypercalcaemia, in which remission occurs spontaneously.

Hypermagnesaemia may be observed after administration of large doses of magnesium sulfate to the mothers for treatment of pre-eclampsia. Clinical features include weakness, depressed or absent tendon reflexes, hypotonia and stupor, and it may lead to respiratory failure (Greenberg et al. 2011). As magnesium sulfate is now more widely used as neuroprotection, this will be seen more often, with apnoeas as a side effect of low blood levels of magnesium (Doyle et al. 2009).

**Other Disturbances of Electrolyte Metabolism**

These are uncommon. Hyponatraemia may be observed with neonatal dehydration or in infants receiving breast milk with a low sodium concentration, but is more common in extremely preterm infants. An increased sodium intake with subsequent hyponatraemia was associated with development of grade II–IV haemorrhage in a large cohort of 722 preterm infants with a birthweight <1500 g (Barnette et al. 2010). Hyponatraemia (<120 mmol/L) with convulsions has been observed in neonates and can be due to a variety of disorders, such as Bartter syndrome, pseudohypoaldosteronism, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and adrenal insufficiency (Marcialis et al. 2011). Non-oliguric hyperkalae mia used to be a common problem in preterm infants with severe neonatal distress of various origins, but is no longer a common problem with improved neonatal care. It may be responsible for disturbances of cardiac rhythm (Vemgal and Ohlson 2012).

**OTHER METABOLIC DISTURBANCES IN THE NEONATAL PERIOD**

It is beyond the scope of this chapter to discuss metabolic disorders, which may present with neonatal encephalopathy and are sometimes referred to as "HIE mimicks" (vitamin B6 deficiency, pyridoxal phosphate deficiency, biotinidase deficiencies; and some important conditions such as glycine encephalopathy (non ketotic hyperglycinemia), molybdenum cofactor and sulphite oxidase deficiency) (Campistol and Plecko 2015). These are dealt with in Chapter 9 and are not discussed here. Many metabolic disorders may present with encephalopathy and/or neonatal seizures and should not be confused with perinatal asphyxia. An extensive family history (consanguinity, miscarriage, stillbirths or early neonatal demise) is of importance. A neurological deterioration usually
These are described in Part 10 of this book. The presence of hypotonia is one of the most frequent neurological signs in newborn infants. Most hypotonic neonates have disorders of the CNS, as many as 82% in the study of Laugel et al. (2008). In such neonates, hypotonia is not accompanied by paralysis and there are usually other signs of CNS involvement such as lethargy, swallowing difficulties and abnormal primary reflexes. Such a picture is seen in HIE and acute neonatal distress of metabolic or infectious origin. Peripheral causes of neonatal hypotonia generally produce some degree of paralysis and often respiratory and swallowing difficulties. Once again a good clinical history is important in making the distinction (Vasta et al. 2005; Laugel et al. 2008). The family history is important, as is the presence of decreased fetal movements and polyhydramnios during pregnancy.

**NEUROMUSCULAR DISEASES**

The lesion spontaneously disappears in a few weeks’ or months. On late X-rays it may produce pseudolacunar images. Cephalhaematomas should not be tapped or evacuated because they disappear spontaneously and these manoeuvres imply a risk of infection. An infection of the cephalhaematoma has been reported but is rare (Zimmermann and Duppenthaler 2016). Subgaleal haemorrhage is not limited to a single bone. The blood may spread beneath the entire scalp and even dissect into tissues of the neck, forehead and eyelids. It often occurs as a consequence of vacuum extraction (Govaert et al. 1992b; Amar et al. 2003) (Fig. 2.24). Coagulation defects, especially vitamin K deficiency and haemophilia, are a frequent complicating factor. When present, the lesion tends to increase in size during the first two to three days and may reach massive proportions with consequent acute anaemia and hyperbilirubinaemia (Govaert et al. 1992b; Govaert 1993). Subgaleal haemorrhage (also wrongly termed ‘giant cephalhaematoma’) may constitute a life-threatening emergency requiring urgent transfusion. A mortality rate of 12% was noted by Kilani and Wetmore (2006). Caput succedaneum is of no pathological significance.

**SKULL FRACTURES**

Linear fractures of the skull are not rare in newborn infants. They are seldom associated with intracranial pathology and are therefore of limited significance, requiring no treatment. A depressed skull fracture (the so-called ‘ping-pong lesion’) usually involves the parietal bones (Zalatimo et al. 2012). Palpation shows a localised depression, but neurological complications...
Injury to the spinal cord is still observed in the newborn infant (Vialle et al. 2008). The frequency is difficult to evaluate. Towbin (1969) found cord lesions in over 10% of all newborn necropsies. This figure is certainly much too low and may be the result of inclusion of extreme congestion or haemorrhagic appearance of the epidural adipose tissue, which is a common finding (Friede 1989). Menticoglou et al. (1995) estimate, based on extrapolation of Towbin’s (1969) data, a prevalence of one per 90 000 live births. Most lesions involve either the lower cervical and upper thoracic cord with breech delivery, or the upper cervical region with cephalic presentation. Vertebral lesions are uncommon. There may be laceration of the meninges and severe destruction of the cord, leaving it severely attenuated with gliosis, cavitation, and destruction of tracts or cells that may affect the whole or part of the cord. Secondary necrosis due to circulatory disturbances has been observed (Adams et al. 1988a).

In a child who presents with hypotonia, a flaccid quadriplegia or low thoracic paraplegia after a difficult delivery, a spinal cord injury must be included in the differential diagnosis (Journeau et al. 2001). Cord injury occurs mostly in breech deliveries and mid-forceps extractions. Excessive longitudinal traction or rotation is the major mechanism. Hyperextension of the fetal head is an important factor. When detected prenatally, Caesarean section is indicated and usually avoids cord damage (Vialle et al. 2008).

The clinical manifestations are variable. Rapid death from respiratory failure may occur. The most common picture consists of paraplegia with massive hypotonia which may mimic a neuromuscular disorder and be accompanied by paradoxical respiratory movements and respiratory insufficiency. The abdomen is soft and bulging, and the bladder is distended and empties with gentle suprapubic pressure. However, pyramidal tract signs are present (sometimes only secondarily) and a sensory level is detectable. The upper limbs may be affected, especially the lower roots of the brachial plexus. Hypotonia may persist or evolve into spasticity. The diagnosis is not always easy, because extrinsic compression and congenital tumours, neuromuscular diseases and spinal cord necrosis secondary to intra-arterial umbilical catheters (Muñoz et al. 1993) may present with similar symptoms. Somatosensory evoked potentials may help determine an equivocal sensory deficit. Imaging of the cord confirms the diagnosis and allows a precise evaluation.

Plain X-rays and low-frequency ultrasonography are the initial modality for evaluation, which can be done at the bedside (MacKinnon et al. 1993). It might show haematomyelia, spinal disruption, extraspinal haematoma and malalignment. MRI provides the best resolution (Mills et al. 2001) and is clearly superior to CT myelography with metrizamide. MRI needs to be performed to facilitate differential diagnosis of oedema, ischaemia and haemorrhage.

The prognosis is poor with persistence of the deficits and occurrence of respiratory or urinary complications (de León et al. 1995). The presence of breathing movements on day 1 was associated with mild disability, whereas the absence of breathing movements on day 1 and little or no recovery of motor function in the first 3 months were associated with permanent total dependency on mechanical ventilation and quadriplegia (MacKinnon et al. 1993). In occasional patients, more limited lesions may be responsible for suspended neurological signs with only mild spasticity of the lower limbs. In such patients the lesion may evolve into true syringomyelia (Yamano et al. 1992). As no treatment is effective, emphasis must be placed on prevention. Patients with paraplegia should be meticulously taken care of and rehabilitated. No evidence was found for the use of methylprednisolone in adults with spinal injury (Hurlbert 2001).

A few patients are on record with probable early prenatal damage to the spinal cord, possibly of vascular origin. The extent of damage was variable, from agenesis of the whole cord to segmental lesions, usually in the cervical region. Ramesh et al. (1989) have described segmental narrowing of the dorsal cord in association with vertebral abnormalities and congenital paraplegia, which they attributed to an early insult to the developing spinal cord and vertebrae. Bode et al. (1994) reported congenital hypoplasia of the medulla oblongata.

**SPINAL CORD INFARCTION**

Spinal cord infarction after catheterisation of the umbilical artery (very seldom the umbilical vein), with or without injection of drugs or fluids, is a rare but dramatic event (Muñoz et al. 1993), probably related to progressive thrombosis or spasm involving the main branch of the anterior spinal artery. A similar adverse event has been reported after an inadvertent intra-arterial injection of viscid material during intramuscular injection. Non-traumatic intramedullary haemorrhage has been recorded (de León et al. 1995).

**INJURY TO NERVES, PLEXUS AND ROOTS**

Brachial plexus injury, the most common peripheral nerve injury in the neonatal period, is discussed in Chapter 25.
Chapter 2  Neurological Diseases in the Perinatal Period

Other injuries to nerves, also described in Chapter 25, are rare in the neonatal period. A typical example is injury to the median nerve as a result of attempts to catheterise the radial or brachial artery at the wrist or elbow for blood gas monitoring. Other examples include the following: injury to the radial nerve as a result of subcutaneous fat necrosis of the upper arm; and laryngeal nerve palsy, probably related to abnormal intrauterine posture with rotation and lateral flexion of the head, causing the thyroid cartilage to compress the superior branch of the nerve against the thyroid bone, and the recurrent nerve against the cricoid cartilage. Vocal cord paresis due to injury to the right laryngeal nerve has been reported after ECMO in neonates with severe respiratory distress (Schumacher et al. 1989).

Diaphragmatic paralysis is associated with brachial plexus injury in 80–90% of cases. When isolated, its diagnosis as a cause of neonatal respiratory distress is made by chest X-rays showing elevation of one or both hemidiaphragms. Stamrood et al. (2009) reported that plication of the diaphragm was required in 10 of 19 infants because of failure to wean from ventilatory support or serious persistent respiratory distress. Infants who failed to wean from ventilatory support and undergo early plication had a quick recovery and could be extubated successfully within a few days.

Left vocal fold paralysis is seen in about 20%–40% of extremely preterm infants after surgical closure of a patent ductus arteriosus. This may result in poor respiratory, feeding and/or developmental outcomes (Benjamin et al. 2010, Rukholm et al. 2012).

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Chapter 2 Neurological Diseases in the Perinatal Period


PART II
Brain Malformations, Neurocutaneous Syndromes, Genetic Anomalies and Dysmorphic Syndromes

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# Developmental Brain Malformations

_Nadia Bahi-Buisson and Nathalie Boddaert_

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CHAPTER 3

Developmental Brain Malformations
Nadia Bahi-Buisson and Nathalie Boddaert

The development of the human cerebral cortex is a complex dynamic process that occurs during several gestational weeks (Gleeson and Walsh 2000). During the first stage, stem cells proliferate and differentiate into young neurons or glial cells deep in the forebrain, in the ventricular and subventricular zones lining the cerebral cavity. During the second stage, cortical neurons migrate away from their place of origin: most cells migrate along the radial glial fibres from the periventricular region toward the pial surface, where each successive generation passes the other and settles in an inside-out pattern within the cortical plate. When neurons reach their destination they stop migrating and order themselves into specific ‘architectonic’ patterns guiding cells to the correct location in the cerebral cortex. This third phase involves the final organisation within the typical six layers of the cortex, associated with synaptogenesis and apoptosis (Barkovich et al. 2012).

Abnormal cortical development is increasingly recognised as a cause of developmental disabilities and epilepsy. This recognition is largely due to improved magnetic resonance imaging (MRI) resolution, which makes it possible to assess the distribution and depth of cortical sulci, cortical thickness, the boundaries between grey and white matter and variations in signal intensity. Abnormalities of any or all of these features may be observed in different malformations of cortical development (MCD), which may be restricted to discrete cortical areas or may, alternatively, be diffuse (Guerrini and Dobyns 2014).

A classification scheme has been developed categorising MCD into three major groups that summarise the main developmental steps as malformations of cell proliferation, neuronal migration, or postmigrational cortical organisation and connectivity. Although the classification of MCD has advanced substantially during the past decade, in practice only a few categories are used, including lissencephaly, polymicrogyria, schizencephaly, focal cortical dysplasia and periventricular nodular heterotopia. However, emerging evidence suggests that MCD are far more heterogeneous than this classification suggests (Guerrini and Dobyns 2014; Parrini et al. 2016).

So far, more than 100 genes have been associated with one or more types of MCD. The biological pathways include cell cycle regulation at many steps (especially mitosis and cell division), apoptosis, cell-fate specification, cytoskeletal structure and function, neuronal migration and basement-membrane function, and many inborn errors of metabolism. A subset of MCD genes – especially those associated with megalencephaly – are associated with postzygotic (i.e. mosaic) mutations (Lee et al. 2012). However, it is important to keep in mind that a significant proportion of acquired causes, mostly viral infections and vascular events may cause morphological brain abnormalities, but have a quite different recurrence risk (Hennekam et al. 2013).

Genetic testing needs accurate assessment of neuroimaging features and familial distribution, if any, and can be straightforward in some disorders but requires a complex diagnostic algorithm in others. Because of substantial genotypic and phenotypic heterogeneity for most of these genes, a comprehensive analysis of clinical, neuroimaging and genetic data is needed to properly define them. Exome sequencing and ultra-high field MRI are rapidly modifying the classification of these disorders (Guerrini and Dobyns 2014).

DISORDERS OF VENTRAL INDUCTION

This term designates those malformations that result from induction failure involving the cephalic mesoderm, the adjacent neuroectoderm and associated neural crest derivatives, and the entodermal anlagen for facial structures. Induction failure is probably time-specific as ventral induction is completed prior to the 33rd post fertilisation day. The major defect is failure of the primary cerebral vesicle (telencephalon) to cleave and expand laterally. Midline facial defects that are frequently associated are a simultaneous consequence of the same defect involving the facial structures. A more detailed description can be found in Chapter 1.

HOLoproencephaly

Holoproencephaly, the most common malformation of the forebrain in humans, is a structural anomaly of the brain...
resulting from failed or incomplete forebrain division in the third to fourth weeks of gestation. The forebrain (prosencephalon) incompletely cleaves into right and left hemispheres, deep brain structures, and the olfactory and optic bulbs and tracts (Solomon et al. 1993; Muenke and Cohen 2000; Lachawan and Muenke 2002; Ming and Muenke 2002; Dubourg 2007). Previously named ‘arhinencephaly’, this term is improper as abnormal development of the rhinencephalic structures and, in particular, absence of the olfactory bulbs and stems can exist in brains with complete separation of the hemispheres (Kobori et al. 1987), although they are virtually always lacking with incomplete forebrain division.

Holoprosencephaly is the most common developmental defect of the forebrain with an incidence of 1 in 250 conceptions and about 1 in every 10 000 at term (Orioli and Castilla 2010). The aetiology includes both genetic and environmental causes (e.g. maternal diabetes, prenatal exposure to ethyl alcohol, retinoic acid [Muenke and Beachy 2000; Cohen and Shiota 2002]).

A generally accepted classification of cerebral defects in humans with holoprosencephaly includes five main subtypes from the most severe to the least severe based on the degree of separation of the cerebral hemispheres (reviewed in Hahn and Barnes 2010):

- Alobar holoprosencephaly, the most severe, in which there is a single ‘mononventricle’ and no separation of the cerebral hemispheres.
- Semilobar holoprosencephaly, in which the left and right frontal and parietal lobes are fused and the interhemispheric fissure is only present posteriorly.
- Lobar holoprosencephaly, in which most of the right and left cerebral hemispheres and lateral ventricles are separated, but the frontal lobes, most rostral aspect of the telencephalon, are fused, especially ventrally.
- Middle interhemispheric fusion variant (syntelencephaly), in which the posterior frontal and parietal lobes fail to separate, with varying lack of cleavage of the basal ganglia and thalami and absence of the body of the corpus callosum but presence of the genu and splenium of the corpus callosum (Barkovich and Quint 1993).
- A septo-preoptic type, in which non-separation is restricted to the septal and/or preoptic regions; described in small case series (Hahn et al. 2010).

Other structural central nervous system (CNS) findings may occur with but are not specific to holoprosencephaly. The most common include anomalies of midline structures (undivided thalami, absent corpus callosum, callosal dysgenesis absent septum pellucidum, and absent or hypoplastic olfactory bulbs and tracts [rhinencephaly] and optic bulbs and tracts) and macrocephaly secondary to hydrocephalus (Rubinstein et al. 1996).

A spectrum of craniofacial anomalies accompanies holoprosencephaly in approximately 80% of affected individuals. The spectrum of facial anomalies ranges from cyclopia, the most severe presentation, to the normal face as seen in individuals. Common clinical features in individuals without obvious findings such as cyclopia, include microcephaly, closely spaced eyes, depressed nasal bridge, single maxillary central incisor and cleft lip and/or palate. Malformations of the nose include complete absence, agenesis of the nasal cartridige and proboscis (flat nose with a single central nostril without nasal bones). Palatal anomalies include various midline and lateral clefts, midline palatal ridge, bifid uvula, high-arched palate and absence of the superior labial frenulum (Solomon et al. 1993, 2010).

An important feature of holoprosencephaly is incomplete penetrance and variable expressivity. Patients carrying defined mutations may not manifest the disease at all, or have a spectrum of defects ranging from mild defects referred to as microforms (hypotelorism, midfacial hypoplasia, a single maxillary central incisor) that are generally non-lethal, to severe (cyclopia, proboscis), which are usually lethal (Shiota and Yamada 2010). It is currently unknown what drives manifestation of holoprosencephaly in genetically at risk individuals, but it has been speculated that other gene mutations and environmental factors may combine as cumulative insults (Ming and Muenke 2002). Currently, there are no effective preventive methods for holoprosencephaly, and children who survive require long-term multidisciplinary care at a significant financial and emotional cost.

**CLINICAL SUBTYPES OF HOLOPROSENCEPHALY**

**Alobar holoprosencephaly** refers to a completely undivided, very small forebrain that assumes the shape of a horseshoe in the concavity of which lies a dorsal sac. This structure contains little neocortex, the concavity of the horseshoe being made of entorhinal cortex. The thalami are fused on the midline (Simon et al. 2000). The brainstem and cerebellum are well developed. Hydrocephalus is often associated.

Such brain anomalies may be associated with extremely severe facial defects and ocular abnormalities. In cyclopia, a rapidly lethal condition, there is a single eye or partially divided eye in single orbit with or without a proboscis above the eye. In cases of ethmocephaly, the nose is absent, replaced by a proboscis that is located above the level of the closely placed orbits. **Cebrocephaly** patients present with closely spaced eyes with an abnormal nose with single nostril. The most frequent type is holoprosencephaly with median cleft lip in which the premaxillary bone anlage is missing. There is marked osseous hypotelorism. Such patients may live for several months or years, in contrast to those affected by the previously mentioned types.

In **semilobar holoprosencephaly**, there is no dorsal sac and the brain is divided into two hemispheres in its posterior part, while anteriorly abnormal transverse convolutions bridge the median fissure. The thalami are fused in the midline. In the most evolved forms, sometimes termed type A semilobar prosencephaly, the two hemispheres seem to be fully separated, even anteriorly. However, interhemispheric bridging is present in the anterior frontal region and there is no corpus callosum.
Chapter 3  Developmental Brain Malformations

Anteriorly, while the splenium may be present. Anteriorly, the cerebral mantle invaginates deeply with both grey and white matter layers crossing the midline after having lined a more or less sinuous ‘interhemispheric’ fissure (Oba and Barkovich 1995). The sinuous fissure may be a cue for the diagnosis by computed tomography (CT) of semilobar holoprosencephaly. MRI permits differentiation of the interhemispheric bridging from a true corpus callosum on sagittal cuts.

Facial appearance can be normal but facial abnormalities commonly found in semilobar holoprosencephaly, comprise closely spaced eyes, anophtalmia or microphthalmia, depressed nasal bridge, absent nasal septum, flat nasal tip, bilateral cleft lip with median process representing the philtrum-premaxilla anlage and midline cleft (lip and/or palate).

**Lobar prosencephaly**, in its fully developed forms, is characterised by almost complete separation of the hemispheres. Probst (1979) prefers not to classify it as holoprosencephaly, but it is included in the latter group by most investigators (Oba and Barkovich 1995). In this form, the hemispheres are fairly well separated; only the most anterior and ventral part is undivided. The genu of the corpus callosum is thin and the frontal horns are often rudimentary. The central grey nuclei are also partially or completely fused. The cases of telencephalic pseudo-monoventricle with a large cavum septum pellucidum in association with atresia of the frontal horns and various other abnormalities (Poll-The and Aicardi 1985) probably belong to this type.

In addition to these classic types, a less common type is now recognised (Lewis et al. 2002; Simon et al. 2002; Takahashi et al. 2003) in which there is failure of separation of the posterior frontal and parietal lobes whereas the frontal and occipital poles are well separated. The term syntenencephaly is used to designate such cases.

The diagnosis of holoprosencephaly is easy when facial abnormalities are present (Burck et al. 1981). In addition to those described above, there may be bilateral cleft lip and palate with hypoplasia of the median tubercle or trigonocephaly with orbital hypotelorism. However, the face may be normal in the less severe forms. Microcephaly is a feature common to most forms unless aqueductal stenosis, with resulting hydrocephalus, is present (Nyberg et al. 1987). Endocrine dysfunction, especially diabetes insipidus (Hasegawa et al. 1990), and adrenal and growth hormone deficiency, can contribute to the mortality and morbidity of holoprosencephaly.

Neuroimaging studies, especially MRI, confirm the diagnosis and permit detailed analysis of the abnormalities including those of the basal ganglia (Simon et al. 2000). Diagnosis can also be made by ultrasonography when the fontanelle is open. Infants with the most severe types rarely survive the neonatal period. Most surviving infants have severe intellectual disability, and develop seizures that are often infantile spasms with hypersynchrony. Neurological manifestations are highly variable, and some patients may survive into adulthood. Developmental delay is present in all individuals with the holoprosencephaly spectrum of CNS anomalies. The degree of delay is variable, correlating with the severity of the brain malformation, but tends to be severe. Seizures are common, and may be difficult to control. Hydrocephalus can occur, and may result in macrocephaly, rather than the more commonly observed microcephaly. Neural tube defects occur in a small proportion of individuals (Solomon et al. 1993, 2010; Levey et al. 2010).

The occurrence of endocrinological abnormalities is possible. Hypothalamic and brainstem dysfunction may lead to swallowing difficulties and instability of temperature, heart rate and respiration. Pituitary dysfunction is manifest by partial or complete panhypopituitarism with abnormal function of any or all of the anterior and/or posterior pituitary hormones, though central diabetes insipidus is by far the most common finding in persons with non-chromosomal, nonsyndromic holoprosencephaly. Short stature and failure to thrive are common, especially in more severely affected children. Growth hormone deficiency and/or chromosome anomalies may in part be responsible for poor growth in some individuals.

Feeding difficulties may be a major problem in children with holoprosencephaly. At least part of the difficulty may derive from axial hypotonia, poor suck as a result of neurological complications, lethargy, seizures and their effects, side effects of medications and lack of interest. Often gastrointestinal reflux, choking and gagging occur with feeds. More common problems include slowness in eating, frequent pauses and frank vomiting with risk of aspiration. Oral-sensory dysfunction may affect feeding especially when associated with textural aversion and labial and lingual weakness. Children with cleft lip and/or palate often have additional difficulties with oral feeding.

The most common teratogen in humans known to cause holoprosencephaly is maternal diabetes mellitus. Infants of mothers with diabetes have a 1% risk (a 200-fold increase) for holoprosencephaly. Other teratogens, including alcohol and retinoic acid, have been associated with holoprosencephaly in animal models, although their significance in humans is not established (Johnson and Rasmussen 2010). More recently, cholesterol-lowering agents (i.e. statins) have been associated with holoprosencephaly, although a causal relationship between prenatal statin use and holoprosencephaly in the infant has not yet been proven (Solomon et al. 1993; Edison and Muenke 2004). Approximately 25–50% of individuals with holoprosencephaly have a chromosome abnormality. Chromosomal abnormalities are nonspecific and either numeric or structural. Numeric chromosome abnormalities include trisomy 13, trisomy 18 and triploidy: holoprosencephaly is seen in approximately 70% of individuals with trisomy 13, which has a birth prevalence of 1:5000. Defects of the corpus callosum have been reported with trisomy 18 (Solomon et al. 2010). Chromosomal microarray (CMA) has identified copy number variants (CNVs) in 10–20% of all individuals with holoprosencephaly. These CNVs can include loci already known to be associated with holoprosencephaly, as well other loci whose relationship to holoprosencephaly is less well understood (Bendavid et al. 2009).
SYNDROMIC HOLOPROSENCEPHALY

Approximately 18–25% of individuals with holoprosencephaly have a pathogenic variant in a single gene causing syndromic holoprosencephaly. At least 25 different conditions in which holoprosencephaly is an occasional finding have been described; the majority of these disorders are rare. These include Pallister–Hall, Rubinstein–Taybi syndrome, Smith–Lemli–Opitz, Meckel syndrome, Hydrocephalus syndrome (with hydrocephalus, polydactyly and other anomalies), facial clefts and brachial amelia and cardiofaciofacial syndromes.

CONDITIONS RELATED TO HOLOPROSENCEPHALY

Arhinencephaly without holoprosencephaly is occasionally encountered at autopsy in the brains of individuals with intellectual disability. Other malformations, especially microgyrias or heterotopias, are associated (Kobori et al. 1987). Holoprosencephaly may be unilateral.

FRONTONASAL DYSPLASIA

The median cleft face syndromes or frontonasal dysplasia are a group of conditions whose visible common denominator is hypertelorism. Several cases are associated with other ventral induction abnormalities, the commonest of which is anterior cranium bifidum. Hypertelorism is a frequent feature in cases of
corpus callosum agenesis, sometimes with cleft lip, bifid nose or similar anomalies. Anterior cephaloceles of various locations may be found, and these are frequently accompanied by extensive cortical and other malformations (Leech and Shuman 1986). A similar picture can obtain with lipomas of the corpus callosum.

**RHOMBENCEPHALOSYNAPSIS**

Rhombencephalosynapsis consists of partial or complete absence of the cerebellar vermis with continuity of the hemispheres across the midline, thought to be due to aberrant dorsal–ventral patterning. The aetiology of rhombencephalosynapsis is unknown. One hypothesis is that rhombencephalosynapsis is caused by dorsal–ventral patterning defects that result in loss of midline and fusion of lateral structures (Sarnat 2000). Alternatively, rhombencephalosynapsis could represent loss of anterior cerebellar anlage cells destined to become the vermis, or from transformation of these anterior cells to a more posterior and/or ventral hemispheric fate. The cerebellar fusion is in some ways comparable with holoprosencephaly in the forebrain, and indeed, these two malformations have been reported in multiple patients, suggesting a shared, but unknown, developmental mechanism (Pasquier et al. 2009, Ishak et al. 2012).

**Malformations of cortical development (MCDs)** are an important cause of epilepsy, intellectual disability and cerebral palsy. In addition, they represent an extremely interesting group of disorders from the perspective of brain development and its perturbations. Many new MCDs have been described in recent years as a result of improvements in neuroimaging, genetic testing and understanding of the effects of mutations on the ability of their protein products to correctly function within the molecular pathways by which the brain functions. In this review, most of the major MCDs are reviewed from a clinical, embryological and genetic perspective (Table 3.1).

Several systems of classification of cortical malformations have been developed during the last 20 years (Barkovich et al. 1996, 2001). The most commonly used and recently updated is that of Barkovich et al. (2012) that divides these malformations into three groups according to the supposed timing of determination and mechanisms of formation of the various types. Group I are malformations secondary to abnormal neuronal and glial proliferation or apoptosis; Group II, malformations secondary to abnormal neuronal migration; Group III, malformations secondary to abnormal postmigrational development, as the process of cortical organisation begins before the termination of neuronal migration.

Table 3.1 shows a simplified form of this classification making it useful in everyday practice, while providing a theoretical basis for posing of academic questions. Other systems based on pathology, clinical presentation or genetic and molecular processes (Sarnat and Flores-Sarnat 2001, 2002, 2004) have been proposed.

From a clinical point of view, separating diffuse and localised or focal cortical malformations may be useful, although they usually share the same neurobiological mechanisms. Diffuse or generalised abnormalities (e.g. lissencephaly) are responsible for generalised seizures, especially infantile spasms, severe neurological signs and intellectual disability. By contrast, localised abnormalities (e.g. focal cortical dysplasias) are mostly responsible for focal epilepsy usually of early onset (Fauser et al. 2006), which may not be accompanied by cognitive or neurological deficits, and have a much better outcome. Only symptomatic therapy is possible for
diffuse cortical abnormalities, whereas effective surgical treatment may be available for most cases of focal dysplasia. Some diffuse abnormalities may result from metabolic defects (e.g. Zellweger syndrome) or chromosomal abnormalities but also from infectious, vascular or toxic insults for polymicrogyria.

The classification of Barkovich et al. (2001) schematically indicates the most likely mechanisms for each type of cortical malformation. The different stages of corticogenesis described above are, in fact, interdependent and overlapping. The fate of precursor cells is determined before they migrate (McConnell and Kaznowski 1991), and this determination has a bearing on the subsequent processes of migration and organisation. Thus, abnormal cells, e.g. in tuberous sclerosis or in some types of ‘cortical dysplasia’, often do not migrate to their normal position and/or fail to establish normal connectivity. Likewise, disorders of cell proliferation are frequently associated with abnormal migration, e.g. in lissencephaly. As a result, it may be difficult to determine which step of cortical development is mainly interfered with in individual cases, and classifications may be to some extent arbitrary. Some disorders do not fit easily in the proposed scheme; e.g. a high proportion of cases of microcephaly may not be disorders of cortical development and may be due to elastic or other mechanisms rather than developmental diseases. Moreover, even in some cortical malformations the mechanisms presumed to be responsible are mostly speculative and it is likely that many cortical developmental abnormalities are due to associations or interactions of several known or unknown mechanisms.

MALFORMATIONS SECONDARY TO ABNORMAL NEURONAL AND GLIAL PROLIFERATION OR APOPTOSIS

This group of malformations is separated into three categories: reduced proliferation or accelerated apoptosis (congenital microcephalies); increased proliferation or decreased apoptosis (megalecephalies); and abnormal proliferation (focal and diffuse dysgenesis and dysplasia) (Table 3.1). Tuberous sclerosis, which belongs to the category of cortical dysgenesis with abnormal cell proliferation but without neoplasia, is described in Chapter 4, because of the prominence of the cutaneous manifestations.

MICROCEPHALY

Congenital microcephaly, an occipital-frontal circumference of equal to or fewer than 2–3 standard deviations (SD) below the age-related population mean, denotes a fundamental impairment in normal brain development (Woods and Parker 2013). All authors admit that children with moderately small heads (between 2 and 3 SD below the mean) are frequently normal, but there is statistically an increased prevalence of mild microcephaly among children with learning disabilities. Intellectual disability may be more common when a small head is associated with growth retardation. However, even patients with head circumference between 3 and 4 SD below the mean may have normal intelligence.

The underlying aetiologies of genetic congenital microcephaly are complex and multifactorial. Depending on the underlying cause, congenital microcephaly can be associated with structural brain malformations (e.g. gyration issues, agenesis of corpus callosum, pituitary abnormalities) or secondary consequences such as craniostenosis (Verloes et al. 1993). Congenital microcephaly can have an environmental or genetic aetiology (Gilmore and Walsh 2013). Cerebral cortical neurons must have developed by mid-gestation although glial cell division and consequent brain volume enlargement does continue after birth. Impaired neurogenesis is, therefore, most obviously reflected clinically as congenital microcephaly (Alcantara and O’Driscol 2014).

Causes of Microcephaly

The aetiology of microcephaly is diverse (Opitz and Holz 1990). Many cases, termed secondary microcephaly, are the result of acquired elastic lesions or other pathological processes incurred during pregnancy or even later, during the period of rapid head and brain growth that takes place in the first years of life. A significant proportion of cases are apparently primary and are mostly of genetic origin (Table 3.2).

Autosomal recessive primary microcephaly (MCPH), historically referred to as Microcephalia vera (also called ‘true’ microcephaly or ‘primary microcephaly’), is a genetically and clinically heterogeneous disease. Patients with MCPH typically exhibit congenital microcephaly as well as intellectual disability, but usually no further neurological findings or malformations. The degree of microcephaly is usually marked (at 3 SD and often 5–6 SD below the mean), with a narrow, receding forehead and a pointed vertex, giving a peculiar clinical and neuroimaging appearance. Paradoxically, individuals with MCPH do not exhibit gross neurological signs, but hyperkinetic behaviour and disturbances of fine motor coordination are frequently present (Accardo and Whitman 1988). Seizures do not occur in typical cases. Some degree of intellectual disability is present but it is usually mild and most children can acquire at least a simplified language. Their microcephaly with grossly preserved macroscopic organisation of the brain is a consequence of a reduced brain volume, which is evident particularly within the cerebral cortex and thus results to a large part from a reduction of grey matter (Verloes et al. 1993; Kaindl et al. 2010).

Primary autosomal recessive microcephalies (MCPH) belong to the same spectrum of disorders to Seckel syndrome (SCKS) spectrum disorders (Verloes et al. 1993, 2013 updated). Both are characterised by microcephaly and the absence of visceral malformations. Although MCHP and SCKS were previously distinguished by height (maximum height in SCKS was equivalent to the minimum height in MCPH), stature is no longer a discriminating feature, leading
Table 3.2 Congenital microcephaly

| Microcephaly with severe intrauterine growth retardation (MIC-IUGR) and short stature |
| Seckel syndrome |
| MOPD syndromes type 1 and 2 |
| Other MIC-IUGR syndromes |

| Microcephaly with variable short stature (severe to mildly short), moderate to severe DD/ID, normal to thin cortex, gyral simplification, +/- callosal hypogenesis |
| Seckel syndrome or autosomal recessive primary microcephaly (MCPH) |

| Microcephaly with mildly short stature or normal growth, mild-moderate DD/ID, normal to thin cortex, +/- gyral simplification, +/- callosal hypogenesis and +/- focal PNH |
| MCPH |

| Microcephaly with mildly short stature or normal growth, severe DD/ID, variable cortical development with gyral simplification or cortical dysgenesis and +/- ACC |
| MIC with diffuse PMG |
| MIC with asymmetrical PMG |
| MIC with atypical cortical dysgenesis |
| MCPH, MIC with diffuse PMG or asymmetrical PMG |
| MIC with diffuse PMG or asymmetrical PMG and ACC |

| Microcephaly with variable anomalies and less well characterised syndromes, +/- gyral simplification, +/- periventricular nodular heterotopia, +/- cerebellar hypoplasia |
| MIC with diffuse periventricular nodular heterotopia |
| MIC with disproportionate cerebellar hypoplasia |
| MIC (extreme) with jejunal atresia |

| Microcephaly with severe DD/ID and evidence of degeneration, with/without mildly short stature, +/- enlarged extra-axial spaces, +/- ACC, +/- atypical cortical dysgenesis |
| MIC with enlarged extra-axial space |
| MIC with enlarged extra-axial spaces and disproportionate cerebellar hypoplasia |
| MIC due to fetal brain disruption with unknown |
| Amish lethal microcephaly |
| MIC-capillary malformation syndrome |

| MIC with lissencephaly (MLIS) – cortex thick, smooth white–grey border |
| Barth MLIS syndrome |
| Norman–Roberts MLIS syndrome |
| MOPD1 variant with three-layer lissencephaly |
| MIC with lissencephaly, cerebellar hypoplasia and Hirschsprung disease |

| MIC with tissue loss and enlarged ventricles (hydrocephalus ex vacuo or hydranencephaly), with/without cortical dysplasia and with/without ACC |
| Fetal brain disruption sequence |
| Familial fetal brain disruption-like syndrome with unknown cause |
| Familial ‘microhydranencephaly’ |

MOPD, microcephalic osteodysplastic primordial dwarfism; MIC, microcephaly; IUGR, intrauterine growth retardation; DD, developmental disorder; ID, intellectual disability; MCPH, microcephaly primary, autosomal recessive; PNH, periventricular nodular heterotopia; MLIS, microlissencephaly; PMG, polymicrogyria; ACC, agenesis of the corpus callosum.

to the conclusion that these phenotypes constitute a spectrum rather than distinct entities.

Diagnosis of microcephaly is characterised by (1) onset during the second trimester of gestation; (2) occipito-frontal head circumference at birth equal to or less than 2 SD below the mean for sex, age and ethnicity; (3) slower than average increase in head circumference after birth. Variable findings in the MCPH-SCKS spectrum disorders include (1) normal brain structure, in the majority; (2) usually mild to moderate cognitive impairment without significant motor
delay in the majority of persons with MCPH and more severe in those with SCKS and MCPH with brain malformations; (3) degree of short stature; (4) craniosynostosis which may be secondary to poor brain growth (Verloes et al. 1993).

The diagnosis of MCPH-SCKS spectrum disorders is based on clinical findings, brain MRI that shows reduced brain volume with grossly normal architecture, family history consistent with autosomal recessive inheritance and molecular genetic testing when available. Primary microcephaly is genetically heterogeneous. Recessive inheritance is the rule. The genes in which biallelic mutation is known to cause MCPH-SCKS spectrum disorders are separated into those that are currently known to be associated with:

**MCPH phenotype only:** MCPH1 (locus name MCPH1), WDR62 (MCPH2), CDK5RAP2 (MCPH3), KNL1 (MCPH4), ASPM (MCPH5), STIL (MCPH7), CEP135 (MCPH8) and CDK6 (MCPH12);

**SCKS phenotype only:** ATR (locus name SCKL1), NIN (SCKL7) and ATRIP;

**MCPH, SCKS and/or intermediate phenotypes:** RBBP8 (locus name SCKL2), CEP152 (MCPH9/SCKL5), CENPJ (MCPH6/SCKL4), CEP63 (SCKL6) and PHC1 (MCPH11).

Most genes known to cause primary microcephaly affect pathways involving neurogenesis: transcription regulation (MCPH1, CENPJ, CDK5RAP2) (Thornton and Woods 2009), cell cycle progression and checkpoint regulation (MCPH1, CENPJ, CDK5RAP2) (Thornton and Woods 2009), centrosome maturation (CDK5RAP2 and CENPJ) (Thornton and Woods 2009), dynein binding and centrosome duplication (NDE1) (Alkuraya et al. 2011; Bakircioğlu et al. 2011), DNA repair (MCPH1) (Thornton and Woods 2009), progenitor proliferative capacity (ASPM and STIL) (Kumar et al. 2009; Passemand et al. 2009), interference with mitotic spindle formation (WDR62) (Bilguvar et al. 2010; Yu et al. 2010), NDE1 (Feng and Walsh 2004), DNA repair deficit (PNKP) (Shen et al. 2010) and PCNT (Griffith et al. 2008). These pathways affect processes – alterations of cell cycle length, spindle positioning or DNA repair efficiency – that affect neurogenesis and, in particular, the cell cycle phases of mitosis. WDR62, ASPM and STIL are spindle pole proteins, suggesting that focused spindle poles are of great significance in neural progenitor cell division.

Microcephaly secondary to mutations of WDR62 has associated cortical malformations (Yu et al. 2010) (Fig. 3.2). Mutations of ARFGEF2 have associated periventricular nodular heterotopia and some individuals with microcephalic osteodysplastic primordial dwarfism have cortical dysgenesis; in addition, dyskinetic movement disorders are one of the clinical features in ARFGEF2 related disorders (de Wit et al. 2009; Ferland et al. 2009). Mutations of other primary microcephaly genes described so far do not have obvious brain anomalies other than simplification of the gyral pattern and hypoplasia of the corpus callosum (Passemand et al. 2009), although few have had pathological analyses. No definable clinico-imaging characteristics have been identified that separate microcephalies caused by mutations affecting different parts of the mitotic cycle.

**MICROLISSENCEPHALY/MICRENCEPHALY**

In other cases of microcephaly, the cortex is abnormally thick and shows only a small number of abnormal convolutions. These cases have been termed microlissencephaly (Barkovich et al. 1998) or oligogryric microcephaly. Microlissencephaly is an extremely rare entity characterised by the combination of extreme primary microcephaly with poor development of the frontal lobes and disordered cortical lamination with absent sulci and gyri. Several subtypes probably exist (Ross et al. 2001) (Table 3.2). Most cases of microlissencephaly are described in consanguineous families suggesting an autosomal recessive inheritance. However, only few affected genes have been identified so far, including biallelic mutations in NDE1, which encodes a multidomain protein that localises to the centrosome and mitotic spindle poles (Alkuraya et al. 2011; Bakircioğlu et al. 2011), mutations in KATNB1 (Hu et al. 2014; Mishra-Gorur et al. 2014) which encodes a microtubule-severing enzyme that localises to microtubules and centrosomes, and in WDR62, which also encodes a centrosomal protein (Bilguvar et al. 2010; Nicholas et al. 2010; Yu et al. 2010), and more recently Citron kinase (CIT), a multidomain protein required for the completion of cytokinesis (Harding et al. 2016). Furthermore, dominant
mutations in tubulin genes, \textit{TUBA1A}, \textit{TUBB2B} and \textit{TUBB3} (Fallet-Bianco et al. 2014) have been identified, further highlighting the critical implication of the microtubule cytoskeleton in microlissencephaly.

Remarkably, most of the genes involved in microlissencephaly are also responsible for microcephaly, suggesting that both conditions belong to the same disease spectrum. Despite significant progress in understanding the underlying genetic bases of these conditions, the causative genes and pathophysiological mechanisms of most microcephaly/microlissencephaly cases remain unknown, which challenges diagnosis, prenatal testing and genetic counselling.

The differential diagnosis with total craniosynostosis does not raise real problems, and the shape of skull, exophthalmia, normal development, signs of increased intracranial pressure and plain X-rays of the skull make the diagnosis obvious. The most important issue in diagnosis is to differentiate acquired (clastic) micrencephaly from genetic types. Marked neurological involvement, severe intellectual disability and a history of abnormal prenatal or perinatal events in the face of moderate microcephaly support a clastic origin, while the reverse features favour a genetic microcephaly. However, clinical features leave considerable room for uncertainty. The demonstration of destructive changes by neuroimaging is of great value. A normal CT, on the contrary, does not exclude an acquired origin.

Antenatal diagnosis may be difficult, especially in the absence of associated malformations, and errors by excess or by default have been frequent (Deter 2016; Leibovitz et al. 2016). Simple measurement of the biparietal diameter is not sufficient as it may be low in fetuses with sagittal craniosynostosis or marked intrauterine moulding. Repeated examinations with full attention to skull shape are essential.

### MACROCEPHALIES

Macrocephaly, like microcephaly, is defined by reference to head circumference, the arbitrary limit of 2 SD above the age norm being often accepted. With this statistical criterion, the definition includes typical individuals as well as a collection of diverse and totally unrelated entities. A majority of the cases of macrocephaly are not due to abnormal brain development but will be considered here as the large head is a common and striking feature. Lorber and Priestley (1981) studied 510 children with head circumference above the 98th centile. Seventy-five per cent of these had hydrocephalus and increased intracranial pressure, 3% had specific syndromes and 20% had primary megalencephaly with normal pressure. Only 13% of this last group had intellectual disability or neurological abnormalities. The major diagnostic consideration is hydrocephalus or pericerebral collections because these may necessitate immediate treatment. Boys outnumbered girls by 4 to 1, and 50% of the patients had a family history of macrocephaly.

The macrocephalies consist of two main groups: megalencephaly, and hydrocephalus and pericerebral collections. The latter group is studied in Chapter 7.

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<th>Table 3.3 Megalencephaly including both congenital and early postnatal</th>
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<td><strong>Megalencephaly with normal cortex</strong> (or presumably normal cortex)</td>
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<td>Familial megalencephaly</td>
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<td>Bannayan–Riley–Ruvalca syndrome, Cowden disease and megalencephaly–autism</td>
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<td>Sotos syndrome with mutations</td>
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<td>Hemimegalencephaly</td>
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<td>Megalencephaly-capillary malformation syndrome, includes megalencephaly-polymicrogyria-polydactyly-hydrocephalus</td>
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<tr>
<td>Thanatophoric dysplasia or Apert syndrome with mutation of FGFR3 (six-layered PMG-like cortex)</td>
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DD, developmental disorder; ID, intellectual disability.

### Megalencephaly

Megalencephaly (MEG) is a developmental disorder characterised by brain overgrowth that occurs due to either increased number or size of neurons and glial cells. The former may be due to either increased neuronal proliferation or decreased apoptosis. The degree of brain overgrowth may be extensive, ranging from generalised MEG affecting the entire cortex – as with mutations in PTEN phosphatase and tensin homolog on chromosome 10 (PTEN) – to unilateral hemispheric malformations as in classic hemimegalencephaly (HME) (Mirzaa and Poduri 2014). Megalencephaly is classically defined as an oversized and overweight brain that exceeds the age-related mean by 2 SDs or more. Clinically, the distinction between megalencephaly (enlarged brain) and macrocephaly (enlarged head overall) relies on neuroimaging examination of the brain and recognition of enlarged cerebral structures. Whereas megalencephaly is associated with specific syndromes, macrocephaly can be caused by a myriad of causes such as hydrocephalus or ventriculomegaly, enlarged extra-axial spaces, and thickened skull bones (Table 3.3). Therefore, the distinction between megalencephaly and macrocephaly is clinically helpful toward accurate diagnosis.

Megalencephaly has long been classified based on pathogenesis into metabolic and non-metabolic (or anatomic) subtypes.
Weaver syndrome, Simpson Golabi Behmel syndrome and nevoid basal cell carcinoma syndrome. Clinical manifestations of megalencephaly are extremely variable and frequently they are absent altogether; most patients have intellectual disability and many have seizures and diffuse neurological abnormalities.

Hemimegalencephaly

Hemimegalencephaly is a severe brain malformation characterised by overgrowth of all or part of a cerebral hemisphere, often with ipsilateral severe cortical dysplasia or dysgenesis, white matter hypertrophy and a dilated and dysmorphic lateral ventricle. The gyral pattern of the affected hemisphere is abnormal, resembling pachygyric or polymicrogyric cortex (Fig. 3.3). In cases that have been studied microscopically (Robain and Dulac 1992; Sarnat and Flores-Sarnat 2001, 2002, 2004; Flores-Sarnat 2002; Salamon et al. 2006), the cellular hypertrophy due to cellular edema or accumulation of metabolic substrates can cause megalencephaly in a wide range of neuro-metabolic syndromes, such as Canavan disease, glutaric aciduria type I and lysosomal storage disorders, among others. A growing number of developmental (or non-metabolic) genetic syndromes are known to be associated with generalised or focal megalencephaly, including HME. Table 3.4 represents a broad overview of genetic disorders where megalencephaly is a defining/diagnostic or common feature. Brain overgrowth in these syndromes varies widely in severity, distribution and co-occurrence of other malformations of cortical development from a mild (and often relatively) enlarged brain with a normal cortex to bilateral megalencephaly with diffuse cortical dysplasia, as discussed below. Finally, reciprocal copy number changes are known to be associated with brain growth dysregulation (i.e. megalencephaly and microcephaly). Other important overgrowth conditions include Sotos syndrome, CLOVES, fibroadipose hypoplasia, isolated macrodactyly, Klippel–Trenaunay syndrome (KTS), and Klippel-Trenaunay syndrome (KTS). Cutaneous VM (capillary, venous, lymphatic), varicose veins, unilateral hypertrophy of bones and soft tissues; ID/SZ rare

<table>
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<tr>
<th>Gene mutations</th>
<th>Inheritance</th>
<th>Syndrome</th>
<th>Clinical findings</th>
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<tr>
<td>PI3K-AKT-MTOR</td>
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<td>Megalencephaly – autism syndrome</td>
<td>Mild dysmorphy, ASD, ID</td>
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<td>PTEN</td>
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<td>Cowden syndrome</td>
<td>Mucocutaneous lesions, malignancy risk</td>
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<td></td>
<td></td>
<td>HME</td>
<td>Macrocephaly SZ, ID</td>
<td>HME, VMEG, MCD, WM abnormalities (ipsilateral)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Post-zygotic/mosaic (rare germ line)</td>
<td>MCAP syndrome</td>
<td>MEG, capillary malformations (polydactyly, syndactyly), segmental somatic overgrowth, connective tissue/ skin laxity ID, SZ, hypotonia</td>
<td>HYD, VMEG, CBTE, PMG, thick CC</td>
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<td></td>
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<td>HME</td>
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<tr>
<td></td>
<td></td>
<td>Somatic overgrowth: CLOVES, fibroadipose hypoplasia, isolated macrodactyly</td>
<td>Variable segmental overgrowth digital anomalies, spinal anomalies, cutaneous vascular malformations; also isolated macrodactyly, some ID</td>
<td>See above</td>
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<tr>
<td></td>
<td></td>
<td>Klippel–Trenaunay syndrome (KTS)</td>
<td>Cutaneous VM (capillary, venous, lymphatic), varicose veins, unilateral hypertrophy of bones and soft tissues; ID/SZ rare</td>
<td>HYD, calcifications, HME (rare)</td>
</tr>
<tr>
<td>PIK3R2</td>
<td>De novo/dominant</td>
<td>MPPH syndrome</td>
<td>Postaxial polydactyly, MEG, ID, epilepsy, tone abnormalities</td>
<td>MEG, perisylvian PMG, HYD, mega CC</td>
</tr>
<tr>
<td>AKT1</td>
<td>Post-zygotic/mosaic</td>
<td>Proteus syndrome (+/- HME)</td>
<td>Asymmetrical and disproportionate hamartomatous overgrowth of multiple tissues, connective tissue and epidermal nevi, dysregulated adipose tissue, VM, hyperostosis, ID (20%) SZ (13%)</td>
<td>Califications abnormalities of the CC, HYD, HME reported in some individuals</td>
</tr>
<tr>
<td>AKT3</td>
<td>De novo/dominant</td>
<td>MPPH syndrome</td>
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<td>See above</td>
</tr>
<tr>
<td>MTOR</td>
<td>Post-zygotic/mosaic</td>
<td>HME</td>
<td>See above</td>
<td>See above</td>
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<tr>
<td>CCND2</td>
<td>De novo/dominant</td>
<td>MPPH</td>
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<td>See above</td>
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ASD, autism spectrum disorder; ID, intellectual disability; MEG, megalencephaly; HME, hemimegalencephaly; SZ, seizures; VMEG, ventriculomegaly; MCD, malformations of cortical development; WM, white matter, MCAp, megalencephaly-capillary malformation syndrome; HYD, hydrocephalus; CBTE, cerebellar tonsillar ectopia; PMG, polymicrogyria; CC, corpus callosum; CLOVES, congenital lipomatous asymmetrical overgrowth of the trunk, lymphatic, capillary, venous and combined-type vascular malformations, epidermal nevi, skeletal and spinal anomalies; VM, vascular malformation; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome.
that seen in agyria–pachygyria or repetitive triphasic complexes (Paladin et al. 1989). The seizures of patients with hemimegalencephaly tend to be refractory to drug therapy (Devlin et al. 2003). Hemispherectomy may control the seizures in up to 85% of cases, provided the other hemisphere is intact.

Dysregulation of two particular critical cellular pathways, the Ras/mitogen-activated protein kinase (MAPK) pathway and the PI3K-AKT-mTOR pathway, appear to account for the largest number of known megalencephaly/hemimegalencephaly syndromes. Mutations responsible for megalencephaly related to the spectrum of PI3K-AKT-mTOR pathway phenotypes includes predominantly postzygotic mutations present in a mosaic pattern. The related megalencephaly syndromes involve almost every organ system in the body including the brain (intellectual disability, autism, epilepsy, hydrocephalus, Chiari malformation), heart and vascular system (conduction defects, heart-great vessel anomalies), skin (capillary malformations, epidermal nevi), connective tissue (skin laxity, joint hypermobility), skeleton (polydactyly, syndactyly) and others. Mutations within the PI3K-AKT-mTOR pathway are associated with the most severe brain overgrowth phenotypes including marked brain overgrowth (head circumference more than 4 SD above the mean) and hemimegalencephaly, a serious medical condition typically associated with severe early onset intractable epilepsy and poor developmental outcome. In addition, these mutations in core components of the PI3K-AKT-mTOR pathway are also responsible for classic hemimegalencephaly and a variety of megalencephaly syndromes including the megalencephaly-capillary malformation syndrome (MCAP) and the megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH). Collectively, these disorders not only overlap molecularly but also share clinical, neuroimaging, and neuropathologic features (for a review see Mirzaa and Poduri 2014).

The differential diagnosis of megalencephaly may be difficult. Hydrocephalus and intracranial collections should be excluded as they may require surgical treatment (Chapter 7). Differentiation of megalencephaly from large heads found in children with normal or near-normal neurodevelopment is usually easy. However, these children constitute a large heterogeneous group. The majority appears to have genetically determined large heads. Lorber and Priestley (1981) found a high incidence of macrocephaly in the parents, especially the fathers, of such children (Lorber and Priestley 1981). DeMeyer (1972) and Day and Schutt (1979) also suggested that ‘simple’ macrocephaly may be dominantly transmitted (DeMeyer 1972; Day and Schutt 1979). Some of these children with macrocephaly have specific learning disorders, the incidence of which may be higher than among children of normal head size. The rate of head growth is particularly rapid in infants under 4 months of age (DeMeyer 1972; Lorber and Priestley 1981). At this stage the diagnosis of hydrocephalus is often suggested, and neuroimaging examination is in order if the rate of increase does not slow down rapidly. In patients without any neurodevelopmental abnormality and a family history of large head, nothing more than careful follow-up is needed.

**Figure 3.3** Representative MRI figure of hemimegalencephaly related to PIK3CA mutation. Note unilateral right polymicrogyria-like cortical dysplasia, without any additional abnormalities in the corpus callosum, white matter or basal ganglia.
However, the possibility of presymptomatic glutaric aciduria (Hoffmann et al. 1991) or another organic acid disorder frequently associated with macrocephaly should be excluded. In children with dolichocephaly (sagittal suture synostosis) the shape of the skull is important to consider as patients with marked skull elongation usually have a head circumference 3 SD or more above the mean, but the shape of the skull is suggestive. In young infants with perinatal illnesses or in older infants who had nutritional problems, ‘catch-up’ growth may temporarily represent a diagnostic problem (Sher and Brown 1975a, b). Neuroimaging should be obtained in cases with persistently divergent head curves or when signs of increased intracranial pressure are present.

**DISORDERS OF MIGRATION**

These malformations are extremely important clinically as they are responsible for a considerable proportion of cases of intellectual disability and of epilepsy. In several cases, they are amenable to treatment, especially focal abnormalities, which may respond to surgery (Arzimanoglu et al. 2016). They are more often a part of a more complex process that not only affects cell migration but is variably associated with abnormalities of cell differentiation and of cortical organisation.

Cell migration can be interfered with by acquired or genetic causes (Barkovich et al. 2001; Lambert de Rouvroit and Goffinet 2001; Gressens 2006; Barkovich et al. 2012). Depending on the date, type and severity of the causal process, the spectrum of migration disorders will manifest as a major form (heterotopias, lissencephaly–pachygyria or polymicrogyria) or a minor disturbance (abnormal lamination of cortex, microdysgenesis) (see Table 3.5). Both may be localised, multifocal or diffuse and variably associated (Barkovich et al. 1996). Localised areas of migration abnormalities are often associated with more diffuse brain changes (Barkovich et al. 1996). An increasing number of genetic migration disorders are being recognised (see below) and may result from chromosomal deletions or gene mutations. These may affect the multiple, yet incompletely known mechanisms, especially the signalling systems that guide cell movements along glial fibres, the adhesion molecules between neurons and glial guides, the stabilisation resulting in the organisation of functional neuronal circuits.

**HETEROTOPIAS**

Heterotopia represent malformations of cortical development in which neurons do not migrate to their proper final location (Barkovich et al. 2012). They are broadly classified by location as periventricular nodular heterotopia, subcortical heterotopia and leptomeningeal heterotopia, the latter currently being difficult to detect by neuroimaging (Guerrini and Parrini 2010).

Periventricular nodular heterotopia (PNH) is the most common group, being identified as variably sized nodules of neurons along the surface of lateral ventricles on neuroimaging or postmortem studies. Histological analysis shows these nodules to exhibit rudimentary lamination, resembling that in the cortex (Garbelli et al. 2009). Traditionally, PNH have been considered a result of impaired neuronal migration (Sarkisian et al. 2008); however, recent evidence suggests that the primary cause may be a disruption of the neuroependyma, which impairs postmitotic neurons from attaching to radial glial cells and, therefore, impairs initiation of the migration process (Ferland et al. 2009).

Isolated heterotopias may remain asymptomatic or give rise to epilepsy or neurological signs (Barkovich and Kjos 1992). They may be located subcortically or in the subependymal region. Subependymal heterotopias were found in about 2% of patients with epilepsy, constituting 20% of cases of malformations of cortical development with epilepsy (Raymond et al. 1994). They are preferentially localised in the posterior part of the brain and may be uni- or bilateral (Dubeau et al. 1995; Aghakhani et al. 2005; Tassi et al. 2005). When unilateral, they are usually sporadic and manifest clinically with focal epileptic seizures. The epileptic activity may originate from the nodules themselves or from the nearby cortex. Resection of the area indicated by invasive EEG, whether it is located within the nodules or in the nearby cortex (Tassi et al. 2005), may allow control of seizures.

**Periventricular Heterotopias**

Periventricular heterotopia is one of the most common malformations of cortical development and causes seizures, dyslexia and psychiatric disturbances (Gonzalez et al. 2013). The most frequent symmetrical manifestation of periventricular nodular heterotopia (PVNH) is located along the walls of both lateral ventricles predominantly in females and results from heterozygous loss of function mutations in the X-linked FLNA gene (Sheen et al. 2001, Parrini et al. 2006). It is associated with high intrauterine and perinatal lethality in hemizygous males presumably from excessive haemorrhage, however, on rare occasions boys and adult hemizygous male carriers of FLNA mutations have been reported (Sheen et al. 2001). The gene product Filamin A is a large cytoplasmic...
### Table 3.5 Malformations due to abnormal neuronal migration

<table>
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<tr>
<th>MALFORMATIONS WITH NEUROEPENDYMAL ABNORMALITIES: PERIVENTRICULAR HETEROOTPIA</th>
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<tbody>
<tr>
<td>Anterior predominate and diffuse periventricular nodular heterotopia</td>
</tr>
<tr>
<td>Diffuse PNH +/- of temporal horns +/- Ehlers–Danlos</td>
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<tr>
<td>Diffuse PNH composed of microdendrites</td>
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<tr>
<td>Diffuse PNH with frontonasal dysplasia</td>
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<tr>
<td>Anterior predominant PNH</td>
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<tr>
<td>Anterior predominant PNH with fronto-perisylvian PMG</td>
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<tr>
<td>Unilateral or bilateral isolated PNH</td>
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<tr>
<td>PNH and agenesis of the corpus callosum</td>
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<td>PNH and Fragile X syndrome</td>
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<thead>
<tr>
<th>Posterior predominant (temporal-trigonal) periventricular nodular heterotopia</th>
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<tbody>
<tr>
<td>Posterior PNH only</td>
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<tr>
<td>Posterior PNH with hippocampal dysgenesis, colpocephaly, anomalies of midbrain tectum or cerebellar hypoplasia</td>
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<tr>
<td>Posterior PNH with posterior PMG</td>
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<tr>
<th>Periventricular heterotopia, not nodular (unilateral or bilateral)</th>
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<tr>
<td>Diffuse periventricular laminar heterotopia</td>
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<tr>
<td>Frontal predominant periventricular laminar heterotopia</td>
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<td>Posterior predominant periventricular laminar heterotopia</td>
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<tr>
<th>Ribbon-like heterotopia, bilateral undulating heterotopic band</th>
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<tr>
<td>Posterior predominant ribbon-like heterotopia</td>
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<td>Diffuse ribbon-like heterotopia</td>
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<tr>
<th>MALFORMATIONS DUE TO GENERALISED ABNORMAL TRANSMANTLE</th>
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</tr>
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<tr>
<td>Anterior predominant or diffuse lissencephaly (Isolated lissencephaly) or SBH</td>
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<td>Baraitser–Winter syndrome with anterior or diffuse LIS–SBH</td>
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<tr>
<th>Posterior predominant or diffuse classic (four-layered) and two-layered (without cell-sparse zone) LIS and SBH</th>
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</thead>
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<tr>
<td>Posterior predominant or diffuse LIS with brainstem and cerebellar hypoplasia, +/- ACC</td>
</tr>
<tr>
<td>Posterior predominant or diffuse LIS (Isolated lissencephaly) or posterior SBH</td>
</tr>
<tr>
<td>Diffuse LIS with hair and nail anomalies</td>
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<tr>
<td>Perisylvian (central) pachygryria (Isolated LIS)</td>
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<tr>
<th>MALFORMATIONS DUE TO ABNORMAL TERMINAL MIGRATION AND DEFECTS IN PIAL LIMITING MEMBRANE</th>
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<tbody>
<tr>
<td>Dystroglycan–laminin complex abnormalities with cobblestone malformation complex, +/- congenital muscular dystrophy</td>
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<tr>
<td>Walker–Warburg syndrome</td>
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<tr>
<td>Muscle–eye–brain syndrome</td>
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<tr>
<td>Congenital muscular dystrophy (CMD) with CBLH (Italian MEB)</td>
</tr>
<tr>
<td>FCMD or FCMD with retinal abnormality (MEB-like)</td>
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<tr>
<td>Posterior predominant COB and CMD</td>
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<tr>
<th>COBBLESTONE MALFORMATION IN CDG SYNDROME</th>
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<tbody>
<tr>
<td>Cobblestone malformation with no known glycosylation defect</td>
</tr>
<tr>
<td>Frontal predominant Cobblestone malformation with GPR56 mutations</td>
</tr>
<tr>
<td>Walker–Warburg syndrome secondary to COL4A1 mutations</td>
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<th>OTHER SYNDROMES WITH CORTICAL DYSGENESIS AND MARGINAL GLIONEURONAL HETEROOTPIA</th>
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<td>Fetal alcohol syndrome</td>
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<td>Galloway–Mowat syndrome</td>
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</table>

PMG, polymicrogyria; ACC, agenesis of the corpus callosum; CBLH, cerebellar hypoplasia; MEB, muscle–eye–brain; FCMD, Fukuyama congenital muscular dystrophy; COB, cobblestone malformation; CDG, congenital disorders of glycosylation.
actin-binding and cross-linking protein of diverse functions including initiation of cell migration and spreading, coagulation and aspects of vessel wall integrity (Baldassarre et al. 2009). Cellular function of Filamin A is further modulated by dimerisation with the homologous protein Filamin B, which may rescue defective Filamin A, depending upon the cellular environment (Baldassarre et al. 2009). Functional MRI indicates that the FLNA-associated ectopic cortical neurons are functionally integrated into motor circuits (Lange et al. 2004).

Cerebral MRI demonstrate a specific FLNA-associated PVNH phenotype with bilateral, predominantly confluent nodular heterotopias extending along the entire length of the lateral walls of both lateral ventricles. It is often associated with an enlarged pericerebellar cerebrospinal fluid space in the presence of normal cerebellar and fourth ventricle anatomy referred to as ‘mega cisterna magna’ (Parrini et al. 2006) (Fig. 3.4).

The phenotype in females with heterozygous FLNA loss of function mutation is highly variable (Lange et al. 2015). Difficult to treat epileptic seizures are the core clinical finding in about 90% of the patients (Parrini et al. 2006). Age at onset may be within the first years of life, but more typically, individuals present during childhood. The severity of the seizure disorder may range from mild (with rare frequency and remission without need of antiepileptic drugs) to intractable seizures. No correlation exists between the extent and severity of the nodular heterotopia seen radiographically and the clinical manifestations. Additional neurological findings are rather discrete and may include deficits in reading, processing speed and executive functions, only detectable in subtle neurocognitive testing in about 80% of patients (Chang et al. 2005). Penetrance in heterozygous FLNA mutation carriers is reduced and asymptomatic PVNH may be detected through predictive carrier testing or incidentally in cerebral MRI as the only manifestation of a FLNA mutation. Less frequent FLNA-associated extracerebral manifestations include persistent ductus arteriosus Botalli in the newborn, chronic obstruction, an Ehlers-Danlos-like phenotype affecting connective tissues, cardiac valve disease as well as chronic obstructive lung disease and oto-palato-digital spectrum skeletal phenotypes (Robertson 2005; Bernstein et al. 2011; Lord et al. 2014).

From a genetic point of view, patients with PVNH are also a heterogeneous group. The classic X-linked form is usually caused by mutations of the FLNA gene. A rare autosomal recessive form is caused by mutations in the ARFGEF2 gene (Sheen et al. 2003, 2004) and is characterised by microcephaly and delayed myelination in addition to PNH. Very recently, missense mutations in NEDD4L mapping to the HECT (homologous to the E6-AP carboxyl terminus) domain of the encoded E3 ubiquitin ligase have been shown to lead to PVNH associated with toe syndactyly, cleft palate and neurodevelopmental delay (Broix et al. 2016). PVNH are found in many syndromes; associations with several single gene disorders, chromosomal anomalies (Guerrini and Parrini 2010) including chromosomal imbalances and submicroscopic genomic copy number variations and some presumably disruptive causes have been published.

From a phenotypic point of view, PVNH is a heterogeneous disorder. Apart from the classic group, 13 additional phenotypes represent almost 50% of patients with PVNH not related to FLNA mutation. These include temporop-occipital PVNH with hippocampal malformation and cerebellar hypoplasia, PVNH with fronto-perisylvian or temporop-occipital polymicrogyria, posterior PVNH with hydrocephalus, PVNH with microcephaly, PVNH with frontonasal dysplasia, PVNH with limb abnormalities, PVNH with fragile-X syndrome, PVNH with ambiguous genitalia, micronodular PVNH, unilateral PVNH, laminar ribbon-like and linear PVNH. Periventricular heterotopias may also be associated with cortical dysplasias (Wieck et al. 2005).

Subcortical Heterotopias
Subcortical heterotopias are irregularly lobulated masses of grey matter that are located primarily in the subcortical white matter of the cerebral hemispheres. Subcortical heterotopia have at least two different morphological configurations (1) the subcortical nodular heterotopia; and (2) the subcortical curvilinear heterotopia. A third type is the mixed subcortical heterotopia (Barkovich 1996, 2000). Associated malformations of the brain are common. The most frequent finding is diminution of the size of the ipsilateral hemisphere and thinning of the overlying cortex with shallow sulci. No differences in the clinical manifestations or in the associated anomalies are identified among these three groups of patients. Recently, a new genetic cause has been identified, in EML1 gene, encoding a microtubule-associated protein in ribbon-like heterotopia in humans (Kielar et al. 2014) (Fig. 3.5).
THE SPECTRUM OF CLASSIC LISSENCEPHALY AND SUBCORTICAL BAND HETEROPTOIA

These migration disorders may be considered to represent different degrees of severity of a basic abnormality of neuronal migration, although they are genetically distinct (Palmini et al. 1993) (Table 3.5). Lissencephaly means a smooth brain. The term agyria–pachygyria is better as the brain is not always smooth (Aicardi 1991). In severe lissencephaly the cortex lacks surface folds (agyria) while milder manifestations include abnormally broad folds (pachygyria) or a heterotopic layer of grey matter embedded in the white matter below the cortex (subcortical band heterotopia, [SBH]) (Barkovich et al. 2012). The precise prevalence of lissencephaly is uncertain but estimates range from 11.7 to 40 cases per million births (Dobyns and Das 1993). The pathogenesis of lissencephaly is best understood in the context of normal cortical development. In humans, primitive neurons (neuroblasts) are generated through mitosis of neural stem cells in the ventricular zone of the fetal brain between 5 and 22 weeks of gestation (Wynshaw-Boris et al. 2010). Post-mitotic neuroblasts undergo radial migration outward from the ventricular zone, guided by radial glial fibres, to populate the cortical plate (Ayala et al. 2007). Slow or arrested migration leads to a thickened cortex with reduced folding (pachygyria or agyria) or the stranded neurons of SBH.

Over the last three decades a growing number of causative genes for lissencephaly has been identified.

Classic Lissencephaly

Classic lissencephaly is distinguished from other forms of lissencephaly by the presence of an abnormally thick (10–20mm), four-layer cortex and, typically, by the absence of other major brain abnormalities (e.g. severe congenital microcephaly, agenesis of the corpus callosum, or cerebellar hypoplasia) (Barkovich et al. 2012; Fry et al. 2014). Classic lissencephaly is sometimes referred to as 'type 1' lissencephaly to differentiate it from cobblestone cortical malformation (Forman et al. 2005). Classic lissencephaly is caused by mutations in three genes: PAFAH1B1 (Reiner et al. 1993), DCX (des Portes et al. 1998; Gleeson et al. 1998) and TUBA1A (Kumar et al. 2010). More recently, mutations in DYNC1H1 and KIF2A were found to be responsible for classic lissencephaly (Poirier et al. 2013; Cavallin et al. 2016).

The neuroimaging appearance of lissencephaly is often graded using a 6-point grading system based on the severity and anterior-posterior gradient of the abnormalities. Only grade I actually deserves the name of lissencephaly; grades 2–4 are cases of pachygyria (Dobyns and Truwit 1995) (Fig. 3.6). At the end of the spectrum, grades 5 and 6 apply to SBH or band heterotopias or ‘double cortex’ (Table 3.6). SBH is a disorder of migration in which a superficial cortex, which may be grossly normal or show an aberrant gyration, is separated by a thin layer of white matter from a band of grey matter whose separation from the underlying white matter is straight (Fig. 3.7).

PAFAH1B1 (also often called LIS1) was the first gene associated with lissencephaly (Reiner et al. 1993). In the 1960s, Miller (1963) and Dieker et al. (1969) reported sibling pairs with multiple congenital abnormalities including lissencephaly (Miller 1963). Patients with Miller-Dieker syndrome (MDS) have severe lissencephaly (grade 1 or 2) associated with dystrophic facial features consisting of a high forehead, small jaw, short upturned nose, protruberant upper lip and bitemporal narrowing. Developmental delay and intellectual disability are usually severe (Dobyns et al. 1991; Cardoso et al. 2003). Additional structural abnormalities occasionally reported in MDS include heart defects, omphalocele, cleft palate and genital anomalies in males. Cytogenetic testing revealed that patients with MDS had subtle chromosomal deletions at band 17p13.3 (Dobyns et al. 1983). The deletions found in MDS patients were frequently de novo and encompassed PAFAH1B1/LIS1 along with several nearby genes including the YWHAE (14-3-3ε) gene (Dobyns et al. 1991; Cardoso et al. 2003). Later on, 65% of patients with isolated lissencephaly sequence (ILS, lissencephaly without other major
congenital anomalies or dysmorphic features) were found to carry deletions (whole gene or partial) or intragenic mutations of PAFAH1B1/LIS1 gene (Lo Nigro et al. 1997; Cardoso et al. 2000). In ILS, the lissencephaly is usually less severe (grades 2–4) but the majority of patients still experience significant developmental delay and intellectual disability (Dobyns et al. 1992; Saillour et al. 2009). Severe motor impairment is common. Patients often present with neonatal hypotonia, which evolves into spastic quadriparesis with truncal hypotonia. Other common features include delayed visual development, postnatal microcephaly and feeding difficulties (Dobyns et al. 1992; Saillour et al. 2009). The facial features of patients with ILS are less dysmorphic than those with MDS, and the former usually lack malformations outside the brain. The severity of the neurological impairment broadly correlates with the extent of the agyria and cortical thickening (Cardoso et al. 2000). Around 83% of patients experience early-onset seizures, typically infantile spasms, and nearly all will eventually develop epilepsy (Saillour et al. 2009). The epilepsy is often drug resistant with around half of patients having daily seizures despite treatment. The EEG in most cases shows high amplitude fast activity of alpha or beta frequency, which can alternate, even on the same tracing, with high amplitude delta or theta slow rhythms that may simulate slow spike–wave complexes or hypsarrhythmia (de Rijk-van Andel et al. 1992; Mori et al. 1994) (Fig. 3.8).

LIS1-related lissencephaly has several distinctive neuroimaging features. These include a smooth, thickened cortex (typically 12–20mm compared with a normal thickness of 3–4mm) with a cell-sparse zone and a ‘posterior to anterior’ (P > A) severity gradient with more severe abnormalities at the back of the brain. Other potential features include enlarged lateral ventricles, mild hypoplasia of the corpus callosum, prominent perivascular spaces and mild hypoplasia of the cerebellar vermis (Pilz et al. 1998; Dobyns et al. 1999; Saillour et al. 2009).

DCX (also known as XLIS) was the second major gene to be associated with classic lissencephaly. DCX mutations cause the full spectrum of classic lissencephaly in males (grades 1–6) while females tend to have SBH (Fig. 3.9). The high rate of DCX-related SBH in females is explained by lyonisation (X chromosome inactivation), that produces two populations of cells in the developing brain of female heterozygotes. DCX mutations explain around 10% of ILS (mostly males),

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diffuse agyria</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse agyria with a few shallow undulations over the frontal and temporal (2a) or occipital (2b) poles</td>
</tr>
<tr>
<td>3</td>
<td>Mixed agyria and pachygyria with either frontal pachygyria and parieto-occipital agyria (3a) or parieto-occipital pachygyria and frontal agyria (3b)</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse or partial pachygyria only, which is more severe posteriorly (4a) or frontally (4b)</td>
</tr>
<tr>
<td>5</td>
<td>Mixed pachygyria (posteriorly 5a; frontally 5b) and subcortical band heterotopia</td>
</tr>
<tr>
<td>6</td>
<td>Subcortical band heterotopia only (posteriorly 6a; frontally 6b)</td>
</tr>
</tbody>
</table>

Modified from Dobyns and Truwitt (1995).

‘Grades 1–6 denote the overall severity of the lissencephaly seen on neuroimaging, with grade 1 being the most severe and grade 6 the mildest form. Grade 1a–6a are more severe posteriorly while grade 1b–6a are more severe anteriorly.'
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Figure 3.7 Typical features of subcortical band heterotopia or double cortex. Representative MRI scans in a 14-year-old girl with a thick continuous band around the entire brain (grades 3–4).

85% of females with sporadic SBH and 25% of males with sporadic SBH (des Portes et al. 1998; Gleeson et al. 1998; Pilz et al. 1998; Leger et al. 2008; Bahi-Buisson et al. 2013). Almost all cases of familial SBH are due to DCX mutations. In familial cases affected mothers may have SBH with mild learning difficulties and epilepsy while their affected male offspring have a more severe grade of lissencephaly. Somatic mosaicism can be an explanation for sporadic SBH in both males and females (Gleeson et al. 2000). Patients with DCX-related lissencephaly have clinical problems similar to those found in patients with PAFAH1 (LIS1)-related lissencephaly. The clinical severity of SBH is dependent on the extent of cortical abnormalities (i.e. the grade of lissencephaly), band thickness and ventricular enlargement (Barkovich et al. 1994). Familial mutations are usually nonsense mutations (Gleeson et al. 1999), whereas patients with de novo mutations are more likely to have truncating mutations (Bahi-Buisson et al. 2013).

Other Forms and Syndromes of Lissencephaly

Several less common variants of lissencephaly are important to recognise because of different genetic and prognostic consequences (Barkovich et al. 2012) (Table 3.5).

Tubulinopathies

TUBA1A mutations are responsible for a spectrum of lissencephaly that ranges from microlissencephaly to perisylvian pachygyria (Keays et al. 2007; Poirier et al. 2007; Bahi-Buisson et al. 2008; Kumar et al. 2010; Cushion et al. 2013; Bahi-Buisson et al. 2014).

TUBA1A-related lissencephaly typically demonstrates a P > A gradient and can be associated with hypoplasia of the cerebellum (mild to severe), dysmorphic basal ganglia, thin or absent corpus callosum, congenital microcephaly. TUBA1A mutations account for 30% of patients with a lissencephaly with cerebellar hypoplasia phenotype and a smaller proportion (1%) of individuals with classic lissencephaly (Kumar et al. 2010).

Following the identification of TUBA1A mutations in lissencephaly patients, heterozygous (and usually de novo) mutations in many neuronally expressed tubulin subunit genes have been associated with a spectrum of malformations of cortical development (Fig. 3.10). These include the β-tubulin genes TUBB2B, TUBB3 and the γ tubulin gene TUBG1 (which is highly-expressed in fetal brain) (Jaglin et al. 2009; Poirier et al. 2010; Poirier et al. 2013). The range of cortical phenotypes associated with tubulin gene defects (the ‘tubulinopathies’) is broad but also shows significant overlap between genes. For example, a small number of TUBA1A mutations have been linked to polymicrogyria-like brain malformations also referred to as ‘dysgyria’ (Bahi-Buisson et al. 2008; Jansen et al. 2011; Oegema et al. 2015). Similarly, there are reports of pachygyria-associated TUBB2B mutations (Cushion et al. 2013). Extra-cortical features such as dysmorphic basal ganglia and abnormalities of the corpus callosum, absence of the anterior commissure and cerebellar dysplasia or hypoplasia are commonly observed in patients with tubulinopathy and are useful diagnostic indicators of tubulin gene involvement (Bahi-Buisson and Cavallin 1993).

X-linked lissencephaly with ambiguous genitalia

X-linked lissencephaly with ambiguous genitalia (XLAG) is a rarer cause of X-linked lissencephaly. XLAG was first described in 1994 in a family with five affected males (Berry-Kravis and Israel 1994). Premature truncation mutations in ARX gene are commonly associated with XLAG. Features in affected males include severe developmental delay, small or ambiguous genitalia, early hypotonia leading to spasticity and early-onset seizures. Other common features include microcephaly, feeding difficulties, growth failure, diarrhoea and temperature instability (Kato et al. 2004). Mortality in the first year is high in affected males, but survival beyond one year has been reported. XLAG can be sporadic or familial. Carrier females may be normal or have intellectual disability, epilepsy and agenesis of the corpus callosum (Bonneau et al. 2002; Kitamura et al. 2002).

Lissencephaly with cerebellar hypoplasia

Lissencephaly with cerebellar hypoplasia is mainly due to de novo mutations in TUBA1A (Kumar et al. 2010). Homozygous mutations in the RELN gene have also been found in a small number of consanguineous families (Hong et al. 2000).
RELN-related lissencephaly with cerebellar hypoplasia has an A > P gradient and is associated with severe abnormalities of the cerebellum and brainstem (Fig. 3.11). Mutations in VLDLR gene which encodes the very low-density lipoprotein receptor, a component of the reelin signalling pathway, have also been described in lissencephaly with cerebellar hypoplasia, although the cortical malformation mainly consists of gyral simplification rather than lissencephaly (Ozcelik et al. 2008).

**Baraitser–Winter syndrome**

Baraitser–Winter syndrome (BWS) is a rare malformation syndrome first described in 1988 (Baraitser and Winter 1988). Patients with BWS have characteristic facial features, which include hypertelorism, broad nose with large tip and prominent root, congenital non-myopathic ptosis, ridged metopic suture and arched eyebrows. Iris or retinal coloboma is frequently present, as is sensorineural deafness. The majority of patients have a degree of anterior–predominant pachygyria. Intellectual disability and epilepsy are common and their severity correlates with the extent of the brain malformations. Recently, gain-of-function missense mutations in two genes, ACTB and ACTG1 have been described in patients with BWS. The typical brain abnormality associated with BWS is pachygyria with an A > P severity gradient (Riviere et al. 2012; Poirier 2015) (Fig. 3.12).

**Microlissencephaly**

Microlissencephaly consists of extreme congenital microcephaly and agyria or pachygyria with a thick cortex. At least five or six types that may be recessively transmitted have been described with variable thickness of the cortex, localisation of any existing sulci, and presence of associated abnormalities such as cerebellar hypoplasia, brainstem atrophy and enlarged ventricles (Ross et al. 2001; Sztiria et al. 2004; Adachi et al. 2011). Some authors separate these cases from oligogyrine microcephaly (Hanefeld 1999), which they consider a form of primary microcephaly rather than a disorder of migration. Clinical features of patients with microlissencephaly include profound cognitive impairment, brain atrophy and extreme microcephaly (head circumference more than 10 SD below the mean). Homozygous mutations in the NDE1 (Nuclear distribution factor E-homolog1) gene have recently been shown to be a cause of microlissencephaly (Alkuraya et al. 2011). Similarly, recessive mutations in KATNB1, which encodes the noncatalytic regulatory p80 subunit of katanin, cause microlissencephaly (Hu et al. 2014; Mishra-Gorur et al. 2014).

**Cobblestone cortical malformation**

Cobblestone cortical malformation (CCM), also known as cobblestone cortex, cobblestone lissencephaly or ‘type 2’ lissencephaly, is clinically, genetically, histologically and neuro-radiologically distinct from classic lissencephaly. CCM can appear agyric or pachygyric, although with higher quality brain imaging an irregular or pebbled aspect to the cortex becomes visible. The cortex in cobblestone cortical malformation...
Figure 3.9  Distinctive MRI pattern of lissencephaly related to LIS1 and DCX mutations. In LIS1 related lissencephaly, the lissencephaly is most prominent in the posterior (parietooccipital regions). By contrast, in DCX related lissencephaly, the lissencephaly is more severe in the frontal and temporal regions.

is typically thinner than in classic lissencephaly (1cm). Irregularity in the grey-white boundary may also be present, similar to that seen in polymicrogyria. Other MRI features include dilated ventricles, white matter abnormalities, brainstem hypoplasia and cerebellar abnormalities including cysts. Histopathologically, cobblestone cortical malformation is due to over-migration of neurons (in contrast to the under-migration of classic lissencephaly). Neurons migrate through breaches in the glia limitans and accumulate in the subarachnoid space giving the cortex a granular surface and a polymicrogyric appearance is frequently visible together with areas devoid of gyri (Haltia et al. 1997). Cobblestone cortical malformation is genetically heterogeneous but is mostly due to autosomal recessive defects in alpha-dystroglycan O-glycosylation. Around half of patients have mutations in POMT1, POMT2, POMGNT1, FKTN, FKRP, and LARGE. Other genes include POMGNT2, TMEM5, POMK, ISPD, GMPPB, GTDC2, B3GNT1 and B3GALNT2 (Vajsar and Schachter 2006; Godfrey et al. 2007; Clement et al. 2008; Mercuri et al. 2009; Chan et al. 2010).

Three major phenotypes are associated with cobblestone cortical malformations: Walker–Warburg syndrome, Muscle-Eye-Brain disease and Fukuyama Congenital Muscular Dystrophy. These disorders demonstrate a combination of eye, muscle and brain abnormalities (Barkovich 1998).

**Walker–Warburg Syndrome**

Walker–Warburg syndrome (WWS) (Vajsar and Schachter 2006) is a rare form of autosomal recessive congenital muscular dystrophy associated with brain and eye abnormalities. WWS has a worldwide distribution. The overall incidence is unknown but a survey in north-eastern Italy has reported an incidence rate of 1.2 per 100,000 live births. It is the most severe form of congenital muscular dystrophy with most children dying before the age of 3 years. WWS presents at birth with generalised hypotonia, muscle weakness, developmental delay with intellectual disability and occasional seizures. It is associated with type II cobblestone lissencephaly, hydrocephalus, cerebellar malformations, eye abnormalities
Figure 3.10  **Tubulinopathies.** Distinct MRI pattern associated with mutations in tubulin genes. (a–c): Four-month-old with classic lissencephaly with a more severe posterior to anterior gradient. (d–f): Fetus at 32 weeks gestation with complete agyria, virtually no sulci and complete corpus callosum agenesis. (g–i): Six-year-old with central pachygyria. The basal ganglia are malformed, appearing as large round structures in which the caudate, putamen and globus pallidus cannot be distinguished (h). Associated malformations include partial agenesis of the rostrum and the splenium (g), thin brainstem and dysplasia of the cerebellar vermis (i). (j–l): Six-year-old with polymicrogyria that appears mildly asymmetrical and most severe over the central regions rather than over the posterior pole. The corpus callosum is hypoplastic (l). The superior vermis is dysplastic (arrow in l).
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and congenital muscular dystrophy characterised by hypoglycosylation of alpha-dystroglycan. The cortex has the appearance of a double cortical layer due to the presence of the subcortical heterotopic islands, which may be striking (Fig. 3.13). The meninges are thick and have a milky appearance due to massive mesenchymal proliferation, especially around the brainstem. The cerebellum is small and lacks a vermis, with cerebellar cortical and subcortical cysts represent small areas of pia/subarachnoid space herniating inward through gaps in the pial limiting membrane. The hypoplastic/dysplastic brainstem has typically an abnormal Z-shaped configuration on sagittal images.

The pyramidal tracts are usually absent, and in 75% of cases hydrocephalus is present. It is usually due to fibrosis of the abnormal meninges, but aqueductal stenosis has been reported (Vajsar and Schachter 2006; Godfrey et al. 2007; Clement et al. 2008; Mercuri et al. 2009). There is often fusion of the frontal poles and of the molecular surfaces of cerebellar lamellae. Microscopically, there is complete disruption of cortical architecture, the cortical plate consisting of a variable thickness of poorly oriented cells separated by trabeculae of gliomesenchymal tissue in continuity with that of the meninges. Multiple islands of heterotopic grey matter are aligned parallel to the cortical surface, separated from the overlying cortex by a thin layer of white matter in which thin blood vessels are tangentially aligned. Fibroglial tissue isolates

Figure 3.11 Reelin related lissencephaly in an 11-month-old girl. (a) The corpus callosum is thin; the pons is reduced in size in antero-posterior extent; (b) the hippocampus appears flattened, lacking definable upper and lower blades; (b and d) the cerebellum is severely reduced in size, with hypoplasia of the inferior vermis and cerebellar hemispheres, devoid of any detectable folia (folds) or normal architecture; (c) the cortex is thickened and the gyral pattern is simplified; the pachygyria is more severe frontally and temporally.

Figure 3.12 Baraitser–Winter syndrome frontally predominant pachygyria in a 4-year 6-month-old boy. The cortex is thickened and the pachygyria is more severe frontally and temporally. Note the shortened and thick corpus callosum.

Figure 3.13 Walker–Warburg syndrome in a 3-year-old boy. Abnormal thickening of the cortex with an aspect close to polymicrogyria (cortical dysplasia), with major ventricular dilatation. Hypoplasia of the corpus callosum, brainstem and cerebellum. Note subcortical white matter hyperintensities.

glomerular or trabecular formations of neural cells (Takashima et al. 1987). The cerebellum is totally disorganised. The vermis is usually missing, and multiple cortical round cysts are seen that can be visualised by MRI (D’Amico et al. 2006). The
clinical features include severe neurological dysfunction from birth; eye abnormalities with retinal dysplasia in all cases, and microphthalmia and anomalies of the anterior segment (Peters anomaly, cataracts, persistence of primitive vitreous body) in most; and the presence in some cases of a posterior cephalocele or large posterior fontanelle. Infants with severe neurological abnormalities and hydrocephalus in association with eye anomalies are highly suspect of having CCM, which is a relatively common cause of genetic hydrocephalus.

Prenatal diagnosis is possible on the basis of hydrocephalus, cephalocele and eye abnormalities (microphthalmia and/or retinal detachment) (Rhodes et al. 1992) and may be confirmed by gene study (Chitayat et al. 1995; Gasser et al. 1998). Muscle involvement is an integral part of cases of CCM (Barkovich 1998), although three patients with normal eyes and muscle has been reported (Dobyns et al. 1996).

**Muscle–Eye–Brain Disease**

In this disease, described by Santavuori et al. 1989, 1998), brain dysfunction is usually less severe. Eye abnormalities mainly consist of severe myopia but may also include such complications as glaucoma and visual failure (Pihko et al. 1995; Haltia et al. 1997). The ventricles are widely dilated and the septum is usually absent (Fig. 3.14). The disease is present at birth but is apparently progressive as shown by the flattening of the ERG after infancy. Flash-evoked potentials are of high amplitude in three-quarters of the patients (Chapter 26).

**Fukuyama Congenital Muscular Dystrophy**

Fukuyama congenital muscular dystrophy is from the neurological point of view a less severe presentation of the cobblestone cortex group, although intellectual disability is marked and eye abnormalities are frequent. The clinical presentation is dominated by muscular impairment (Chan et al. 2010) (see Chapter 21).

The prognosis of the CCM is poor, especially that of the Walker–Warburg type. Most affected infants die in a few weeks or months, an occasional patient living to a few years. Patients with severe hydrocephalus should receive a shunt to avoid monstrous growth of the head, but the ultimate prognosis remains dismal. However, the outcome of
muscle–eye–brain disease and of Fukuyama dystrophy is less severe, and a spectrum of severity from lethal cases to cases of congenital muscular dystrophy or even limb–girdle dystrophy with normal brain and cognition may be observed.

Kallmann Syndrome

A peculiar migration abnormality is the cause of the Kallmann syndrome, comprising anosmia due to the absence of olfactory bulb stalks and gyri, hypogonadism, and often mild intellectual disability. This syndrome is genetically heterogeneous but usually transmitted as an X-linked recessive trait. Two genes (\textit{KALIG1}, localised to Xp22.3, and \textit{KALIG2}, a fibroblast growth factor receptor \textit{[FGFR1]} gene), confirm the genetic heterogeneity (Sato et al. 2004; Albuisson et al. 2005). The migration defects involve the olfactory axons and gonadotrophin releasing hormone-secreting neurons that originate from the olfactory placode and normally migrate through the ethmoid to the olfactory bulbs, which do not develop if not reached by axons. The migration of these cells in Kallmann syndrome is blocked in the nasal area because of lack of adhesion molecules, which play a major role in olfactory axon development. Absence of the olfactory bulbs can be visualised by MRI (Truwit et al. 1993).

Cobblestone malformations comprise a broad spectrum of clinically and genetically overlapping disorders resulting from defects in the pial limiting membrane and the attachment of radial glial fibres thereto. The Walker–Warburg phenotype represents the severe end of the spectrum with profoundly small and dysmorphic cerebellar hemispheres often with cysts, absent vermis and very small brainstem, as well as other major brain malformations: cerebral cobblestone cortex, abnormal white matter, anomalous corpus callosum, enlarged dysplastic tectum, and hypoplastic/dysplastic brainstem (Fig. 3.13). The cerebellar cortical and subcortical cysts represent small areas of pia/subarachnoid space herniating inward through gaps in the pial limiting membrane. Patients frequently have hydrocephalus, eye abnormalities (microphthalmia, optic nerve hypoplasia, chorioretinal coloboma, cataract, glaucoma and/or high myopia), seizures, hypotonia and/or muscular dystrophy. The muscle–eye–brain phenotype represents more moderately affected patients with cerebellar and brainstem hypoplasia, and Fukuyama muscular dystrophy represents the mild end of the spectrum that still includes brain malformation. Recessive mutations in multiple genes (\textit{POMT1}, \textit{POMT2}, \textit{POMGNT1}, \textit{FKTN}, \textit{FKRP}, \textit{LARGE}, \textit{ISPD} and \textit{GTDC2}) can cause overlapping phenotypes across the entire spectrum of disease, but a substantial proportion of patients remain unexplained (Vajsar and Schachter 2006; Godfrey et al. 2007; Clement et al. 2008; Chan et al. 2010; Luo et al. 2012).

MALFORMATIONS DUE TO ABNORMAL CORTICAL ORGANISATION

According to the classification of Barkovich (2012), this category also includes some disorders of late migration. As in the other categories, some of the conditions included depend on mechanisms other than disturbed organisation. Many cases of focal cortical dysplasia, e.g. show abnormal cells of both neuronal and glial origin, indicating abnormal cell differentiation.

POLYMICROGYRIA

Polymicrogyria (PMG) is one of the most common brain malformations accounting for almost 20% of all MCD (Leventer et al. 2010; Stuttorp and Leventer 2014). Polymicrogyria (PMG) refer to an abnormal appearance of cortical gyri that seem to be crowded, too narrow, and form an abnormal convolutional pattern (Fig. 3.15). Synonymous terms include micropolygyria (Haberland and Brunngraber 1972) and microgyria (Crome and France 1959). PMG is not a single entity but a spectrum of cortical malformations with the
be lined by PMG to be called schizencephaly as opposed to porencephalic cysts, which are lined by white matter or gliosis. There is no uniform system of classification for PMG. It has been classified according to imaging patterns (Barkovich 2010; Leventer et al. 2010), histopathological appearance (Friede 1989), and the presumed timing of the aetiology in cortical development (Barkovich et al. 2012). There is a wide spectrum of both the type and severity of the clinical sequelae. PMG can be caused by both genetic and non-genetic causes, with multiple chromosomal loci and causative genes described in recent years. It can be seen as an accompanying feature in numerous genetic syndromes (Jansen and Andermann 2005) (Tables 3.7 and 3.8). PMG may show a variety of histological patterns, but all show abnormal cortical lamination, excessive folding and fusion of adjacent gyri through fusion of the molecular layer. Both unlayered (also known as two-layered) and layered forms of PMG are described. Occasionally, both forms are found in the same patient, suggesting that they may be variations of the same malformation. The layered form may show either four or six layers (Judkins et al. 2011). At the boundaries of layered PMG there is an abrupt transition to normal cortex (Kuzniecky et al. 1993). The MRI feature of microgyri and microsulci is ‘stippled’ grey–white junction (Leventer et al. 2010). Stippling of the grey–white junction is a specific feature of PMG not seen in other MCD. In younger children the polymicrogyric cortex may appear thinner than at later ages. This is thought to be due to the immature state of myelination in subcortical and intracortical fibres (Takanashi and Barkovich 2003).

Once the myelination is complete follow-up MRI may be required to appreciate the full extent of PMG. T2 signal within the cortex is usually normal, although there may be delayed myelination. High T2 signal in the underlying white matter should raise the question of an in utero infection (such as cytomegalovirus) (Fig. 3.16) or a peroxisomal disorder (Fig. 3.17) (van der Knaap and Valk 1991). Polymicrogyria has been described in several topographic patterns (Guerrini and Dobyns 2014). The most common by far is bilateral perisylvian polymicrogyria (Leventer et al. 2010), which varies from the posterior perisylvian region only (grade 4), to the entire perisylvian region (grade 3), to the perisylvian region with extension to other brain regions but not the poles (grade 2), to most of the brain including either or both the frontal or occipital poles (grade 1). However, the perisylvian regions are always the most severely affected. Furthermore, perisylvian polymicrogyria can be bilateral symmetrical, bilateral asymmetrical, or unilateral. Other patterns are almost always bilateral and symmetrical, and include generalised (Chang et al. 2004), frontal (Guerrini et al. 2000), posterior (probably), mesial parieto-occipital, and rare diffuse parasagittal polymicrogyria (Guerrini et al. 1997). Polymicrogyria also occurs in overlying periventricular nodular heterotopia (Wieck et al. 2005).

The clinical manifestations of polymicrogyria vary widely, and depend on several factors. The most severe outcomes...
Table 3.7 Malformations due to abnormal postmigrational development

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<tr>
<th>Malformations with PMG or Cortical Malformations Resembling PMG</th>
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<tbody>
<tr>
<td>PMG (classic) with transmantle clefts (schizencephaly) or calcification</td>
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<tr>
<td>Schizencephaly</td>
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<tr>
<td>Septo-optic dysplasia with schizencephaly</td>
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<td>Schizencephaly with positive neonatal CMV testing</td>
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<tr>
<td>Diffuse or patchy PMG with periventricular calcifications and positive neonatal CMV testing</td>
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<tr>
<td>Diffuse, patchy or perisylvian PMG with hearing loss and positive neonatal CMV testing</td>
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<tr>
<td>Familial schizencephaly with single unilateral or bilateral clefts</td>
</tr>
<tr>
<td>Familial schizencephaly with multiple bilateral clefts</td>
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<td>Band-like calcifications with PMG (pseudo-TORCH)</td>
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<tr>
<th>Polymicrogyria without clefts or calcifications classified by location</th>
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<tbody>
<tr>
<td>Generalised PMG</td>
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<tr>
<td>Frontal PMG</td>
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<tr>
<td>Perisylvian PMG</td>
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<tr>
<td>Posterior lateral parieto-occipital PMG</td>
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<td>Parasagittal PMG</td>
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<tr>
<td>Parasagittal mesial occipital PMG</td>
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<tr>
<td>Hemispheric PMG</td>
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<td>Focal PMG</td>
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<tr>
<th>Syndromes with PMG (neuropathology may differ from classic PMG)</th>
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<tr>
<td>Adams–Oliver syndrome</td>
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<tr>
<td>Joubert syndrome and related disorders with PMG, includes Meckel–Gruber, Arima (cerebro-oculo-renal)</td>
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<tr>
<td>Aicardi syndrome</td>
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<tr>
<td>Oculocerebrocutaneous (Delleman) syndrome</td>
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<tr>
<td>Fronto-parietal PMG, variable ACC and delayed myelination of anterior limb internal capsule</td>
</tr>
<tr>
<td>Knobloch syndrome with high myopia, vitreoretinal degeneration, occipital cephalocele and variable PMG</td>
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<tr>
<td>Aniridia, variable temporal PMG, absent anterior commissure and pineal gland, and variable CBLH</td>
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<tr>
<td>Goldberg–Shprintzen (megacolon) syndrome</td>
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<tr>
<td>Generalised (vs perisylvian) PMG, ACC and optic nerve hypoplasia</td>
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<tr>
<td>Perisylvian PMG, ACC, delayed myelination of anterior limb internal capsule and cerebellar vermian hypoplasia</td>
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<td>Wärburg Micro syndrome</td>
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<tr>
<th>Cortical Dysgenesis Secondary to Inborn Errors of Metabolism</th>
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<tr>
<td>Mitochondrial and pyruvate metabolic disorders</td>
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<tr>
<td>Non-ketotic hyperglycinemia</td>
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<td>Multiple Acyl-CoA dehydrogenase deficiency (Glutaric aciduria type II)</td>
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<th>Peroxisomal disorders</th>
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<tr>
<td>Zellweger syndrome</td>
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<tr>
<td>Neonatal adrenoleukodystrophy</td>
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<tr>
<td>D-Bifunctional protein deficiency</td>
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PMG, polymicrogyria; CMV, cytomegalovirus infection; ACC, agenesis of corpus callosum; CBLH, cerebellar hypoplasia.

occur in children with severe microcephaly (−3 SD or smaller), abnormal neurological examination, widespread distribution of polymicrogyria and additional brain malformations (especially cerebellar hypoplasia). The best outcomes are in individuals who have localised unilateral polymicrogyria without other malformations. Bilateral perisylvian polymicrogyria with oromotor dysfunction (congenital suprabulbar palsy), intellectual disability and epilepsy were described
### Table 3.8 List of genes involved in polymicrogyria

<table>
<thead>
<tr>
<th>Type of Genotype</th>
<th>Gene</th>
<th>Location</th>
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<tbody>
<tr>
<td>Autosomal dominant</td>
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</tr>
<tr>
<td>Megalencephaly – polymicrogyria</td>
<td>AKT3</td>
<td>1q43-q44</td>
</tr>
<tr>
<td>polymicrogyria – hydrocephaly (MPPH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral perisylvian PMG/MPPH</td>
<td>PIK3R2</td>
<td>19p13.11</td>
</tr>
<tr>
<td>Megalencephaly – capillary malformation</td>
<td>PIK3CA</td>
<td>3q26.32</td>
</tr>
<tr>
<td>– polymicrogyria (MCAP)</td>
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<td></td>
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<tr>
<td>PMG and schizencephaly</td>
<td>COLA4A1</td>
<td>13q34</td>
</tr>
<tr>
<td>PMG-like, microcephaly, ACC</td>
<td>DYNC1H1</td>
<td>14q32.31</td>
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<tr>
<td>Bilateral asymmetrical anterior</td>
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<tr>
<td>predominant PMG</td>
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<td></td>
</tr>
<tr>
<td>PMG-like, microcephaly, ACC, CBLH</td>
<td>TUBB</td>
<td>6p21.33</td>
</tr>
<tr>
<td>PMG-like, microcephaly, ACC, CBLH</td>
<td>TUBB3</td>
<td>16p24.3</td>
</tr>
<tr>
<td>Bilateral PMG</td>
<td>KIF5C</td>
<td>2p23.1</td>
</tr>
<tr>
<td>PMG and ACC, microcephaly</td>
<td>TBR2</td>
<td>3p21.3p21.2</td>
</tr>
<tr>
<td>PMG and aniridia</td>
<td>PAX6</td>
<td>11p13</td>
</tr>
<tr>
<td>Persylvian PMG and CHARGE syndrome</td>
<td>CHD7</td>
<td>8q12.1q12.2</td>
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<tr>
<td>Generalised PMG</td>
<td>NHEJ1</td>
<td>2q35</td>
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<tr>
<td>Autosomal recessive</td>
<td></td>
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<tr>
<td>Bilateral frontoparietal PMG</td>
<td>GPR56</td>
<td>16q13</td>
</tr>
<tr>
<td>Temporo-occipital PMG</td>
<td>FIG4</td>
<td>6q21</td>
</tr>
<tr>
<td>PMG and microcephaly</td>
<td>RITN</td>
<td>18q22.2</td>
</tr>
<tr>
<td>PMG and microcephaly</td>
<td>NDE1</td>
<td>16p13.11</td>
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<tr>
<td>PMG and microcephaly</td>
<td>WDR62</td>
<td>19q13.12</td>
</tr>
<tr>
<td>PMG and fumaric aciduria</td>
<td>FH</td>
<td>1q43</td>
</tr>
<tr>
<td>PMG and ‘band-like calcification’</td>
<td>OCLN</td>
<td>5q13.2</td>
</tr>
<tr>
<td>PMG and Wärburg Micro syndrome</td>
<td>RAB3GAP1</td>
<td>2q21.3</td>
</tr>
<tr>
<td>PMG and Wärburg Micro syndrome</td>
<td>RAB3GAP2</td>
<td>1q41</td>
</tr>
<tr>
<td>PMG and Wärburg Micro syndrome</td>
<td>RAB18</td>
<td>10p12.1</td>
</tr>
<tr>
<td>PMG-like, microcephaly, ACC, CBLH</td>
<td>TUBA8</td>
<td>22q11.21</td>
</tr>
<tr>
<td>PMG-like, microcephaly, ACC</td>
<td>TBR2/</td>
<td>3q24.1</td>
</tr>
<tr>
<td>EOMES</td>
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<td></td>
</tr>
<tr>
<td>PMG and Goldberg–Shprintzen syndrome</td>
<td>KIAA1279</td>
<td>10q21.3</td>
</tr>
<tr>
<td>PMG and CEDNIK syndrome</td>
<td>SNAP29</td>
<td>22q11.21</td>
</tr>
<tr>
<td>PMG and Knobloch syndrome</td>
<td>COL18A1</td>
<td>21q22.3</td>
</tr>
<tr>
<td>X-linked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMG and rolandic seizures, oromotor</td>
<td>SRPX2</td>
<td>Xq21.33q23</td>
</tr>
<tr>
<td>dyspraxia</td>
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</tr>
<tr>
<td>PMG and CK syndrome</td>
<td>NSDHL</td>
<td>Xq28</td>
</tr>
<tr>
<td>Chromosomal abnormalities</td>
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<td></td>
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<tr>
<td>PMG</td>
<td>–</td>
<td>lp36.3pter</td>
</tr>
<tr>
<td>PMG and microcephaly</td>
<td>–</td>
<td>1q44qter</td>
</tr>
<tr>
<td>PMG and facial dysmorphisms</td>
<td>–</td>
<td>2p16.1p23</td>
</tr>
<tr>
<td>PMG and microcephaly, hydrocephalus</td>
<td>–</td>
<td>4q21q22</td>
</tr>
<tr>
<td>PMG</td>
<td>–</td>
<td>21q2</td>
</tr>
<tr>
<td>PMG</td>
<td>–</td>
<td>6q26q27</td>
</tr>
<tr>
<td>PMG</td>
<td>–</td>
<td>13q3</td>
</tr>
<tr>
<td>PMG</td>
<td>–</td>
<td>18p11</td>
</tr>
<tr>
<td>PMG and Di George syndrome</td>
<td>–</td>
<td>22q11.2</td>
</tr>
</tbody>
</table>

PMG, polymicrogyria; ACC, agenesis of corpus callosum; CBLH, cerebellar hypoplasia; CEDNIK, cerebral dysgenesis, neuropathy, ichthyosis and keratoderma.
as congenital bilateral perisylvian syndrome (Kuzniecky et al. 1993). A small group of patients have unilateral perisylvian polymicrogyria and present with mild hemiparesis or seizures. Although their developmental and neurological deficits are typically less severe than those of patients with bilateral disease, they can develop intractable seizures and epilepsy with continuous spikes and waves during sleep (Kuzniecky et al. 1994). A wider spectrum of manifestations with both severe seizures including infantile spasms and milder cases presenting with language disorder (Saletti et al. 2007) has been reported in infants. Arthrogryposis of central origin is present in some patients (Poduri et al. 2010; Kuzniecky et al. 1994) (Fig. 3.18).

The clinical features of schizencephaly are extremely variable, and the severity of clinical features correlates with the importance of anatomical anomalies, being greater with open-lip clefts (Denis et al. 2000; Govaert 2009). Bilateral, open defects give rise to severe involvement (Barkovich and Kjos 1992). Some patients have quadriplegia and profound encephalopathy. Unilateral clefts usually manifest with hemiplegia and/or focal epilepsy (Caraballo et al. 2004). With the use of neuroimaging it has been realised that many cases are much less severe, with mild intellectual disability, congenital hemiplegia, a large head or even isolated partial seizures. The involvement of both sylvian and insular regions can be responsible for a biopercular syndrome with facial apraxia and speech difficulties (Becker et al. 1989). Epilepsy is present in about 80% of patients (Granata et al. 1996).

The pathogenesis of polymicrogyria is not understood and is probably variable in relation to its remarkable causal heterogeneity with evidence of extrinsic (i.e. non-genetic) and genetic causes. The substantial pathological, neuroimaging, and clinical heterogeneity suggest that polymicrogyria is not a single malformation per se, but can be grouped by diverse phenotypes (Guerrini and Dobyns 2014). Extrinsinc causes include polymicrogyria related to known or presumed vascular or infectious causes. Several of the earliest descriptions of polymicrogyria came from studies of schizencephaly (Levine et al. 1974), which is associated with extrinsic causes such as vascular insufficiency (especially during twin pregnancies) and cytomegalovirus infections (Barkovich and Lindan 1994). Both causes can result in polymicrogyria without clefts. Some copy number variants have been associated with polymicrogyria, but only deletions in 1p36.3 and 22q11.2 are common (Dobyns et al. 2008). Indeed, when these two loci are excluded, copy number variants seem to be rare. The causal gene has not been identified for any of these loci. All types of single gene inheritance have been reported for polymicrogyria, including several families with autosomal dominant inheritance and some families with rare autosomal recessive forms (Guerreiro et al. 2002). Several reports have described X-linked forms, although the lack of substantiation of these findings throws doubt on the role of these loci in polymicrogyria (Guerrini and Dobyns 2014).

Several syndromes with diffuse or bilateral frontal predominant polymicrogyria have been described. Because pathological changes have not been defined for most of these disorders, it is not clear whether these syndromes are true polymicrogyria or polymicrogyria-like cortical malformations. Polymicrogyria-like cortical malformations have been reported with several metabolic diseases with severe phenotypes, including Zellweger syndrome, neonatal adrenoleukodystrophy, fumaric aciduria, mitochondrial diseases, glutaric aciduria type 2, maple-syrup-urine disease and histidinaemia. However, the histopathology differs from classic polymicrogyria for several of these disorders, especially the peroxisomal disorders and glutaric aciduria type 2 (Guerrini and Dobyns 2014).

**FOCAL CORTICAL DYSPLASIAS**

Focal cortical dysplasias (FCDs) are highly epileptogenic brain lesions and are a frequent cause for drug-resistant focal epilepsies in humans. FCDs present with variable histopathological patterns, including architectural, cytoarchitectural or white matter abnormalities (Taylor et al. 1971). Pathomechanisms compromising neuroblast proliferation, migration or differentiation are likely to play a role in the aetiology of FCD variants. FCDs were subsumed, therefore, into the broad spectrum of malformations of cortical development. Such lesions are increasingly recognised...
using high-resolution MRI. Tailored surgical resections provide favourable seizure control in many patients. The International League Against Epilepsy (ILAE) therefore initiated an ad-hoc task force to review published work and to redefine clinicopathological FCD subtypes (Spreafico and Blümcke 2010; Blümcke et al. 2011; Blümcke and Spreafico 2011).

The morphological spectrum of FCD variants is broad (Desikan and Barkovich 2016). In 2004, the seminal classification system developed by Palmini et al. (2004) distinguished two subtypes. With this system, however, presurgical neuroimaging, electroclinical assessment, and histopathological examination of surgical specimens have not enabled reliable identification of all FCD variants.

By contrast, Palmini type 1 FCDs are histopathologically less well characterised; they occur as isolated lesions in adults or children, and affect one or more lobes, or are associated with a second type of pathological change. Appearances on MRI might be nonspecific, with some lesions appearing only as a grey–white matter interface abnormality and others only as hypoplastic cortical lobes. Additionally, there is no international consensus on applied terminologies, which means that comparisons between published studies are difficult.

With the advances of neuropathological and MRI techniques, an international consortium from different medical and scientific disciplines redefined clinicopathological FCD subtypes, combining histopathological findings, neuroimaging and electroclinical data as classifying parameters.

The ILAE task force (Blümcke et al. 2011) has proposed a new classification of three FCD subtypes (Table 3.9). Type 1 refers to FCDs that are not adjacent to or associated with any other lesion (isolated subtype). Vertical or horizontal cortical dyslamination affecting one or more lobes is the classifying parameter, whereas dysmorphic neurons or balloon cells are absent. Neither pathogenetic data nor specific neuroimaging findings are yet available. The second FCD variant is identical to that introduced by Taylor and co-workers (Taylor et al. 1971) and was termed FCD type 2. Dysmorphic neurons and balloon cells remain the classifying morphological landmarks for this variant. A novel ILAE type 3 FCD subgroup refers to those variants with cortical dyslamination that are adjacent to or associated with other principal lesions. Prominent examples include hippocampal sclerosis (type 3a), glioneuronal tumours (type 3b), vascular malformations (type 3c) and other brain injuries that are acquired during early life (e.g. trauma, ischaemic injury, encephalitis).

### Table 3.9 Focal cortical dysplasias

<table>
<thead>
<tr>
<th>Focal cortical dysplasia (FCD) type 1 (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a: FCD with abnormal radial cortical lamination</td>
</tr>
<tr>
<td>1b: FCD with abnormal tangential cortical lamination</td>
</tr>
<tr>
<td>1c: FCD with abnormal radial and tangential cortical lamination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCD type 2 (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a: FCD with dysmorphic neurons</td>
</tr>
<tr>
<td>2b: FCD with dysmorphic neurons and balloon cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCD type 3 (associated with principal lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a: Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis</td>
</tr>
<tr>
<td>3b: Cortical lamination abnormalities adjacent to a glial or glioneuronal tumour</td>
</tr>
<tr>
<td>3c: Cortical lamination abnormalities adjacent to vascular malformation</td>
</tr>
<tr>
<td>3d: Cortical lamination abnormalities adjacent to any other lesion acquired during early life (e.g. trauma, ischaemic injury, encephalitis)</td>
</tr>
</tbody>
</table>

### ABNORMALITIES OFTEN ASSOCIATED WITH DISORDERS OF CORTICAL DEVELOPMENT

Several deformities often coexist with migration disorders. However, they may also occur in isolation or in association with other malformations. They include agenesis of the corpus callosum, schizencephaly (‘true’ porencephaly), septo-optic dysplasia and colpocephaly.

### AGENESIS AND DYSGENESIS OF THE CORPUS CALLOSUM

Agenesis of the corpus callosum (ACC) is an exceedingly heterogeneous condition that can result from disruption of numerous developmental steps from early midline telencephalic patterning to neuronal specification and guidance of commissural axons. It can occur as an isolated finding on MRI, but is more commonly associated with a broader disorder of brain development (Schell-Apacik et al. 2008; Tang et al. 2009).

ACC encompasses either total absence (complete ACC) or absence from birth of at least one, but not all, of the anatomically defined regions of the corpus callosum (partial ACC), which results in a shorter anterior–posterior length. Hypoplasia denotes a corpus callosum that is thinner than usual, but has a normal anterior–posterior extent although this may be hard to quantitate (Hetts et al. 2006; Palmer and Mowat 2014). Atypical forms, difficult to separate from holoprosencephaly, may be encountered (Barkovich and Norman 1988). Callosal agenesis is relatively common. Its prevalence
in the general population is incredibly varied and ranges from 0.5 per 10,000 in the general population to 230–600 per 10,000 in children with neurodevelopmental disability which would make it one of the most common brain malformations (Jeret et al. 1987).

The absent callosal commissure is usually replaced by two longitudinal bundles, known as longitudinal corpora callosa or Probst bundles, that course on the inner aspect of the hemispheres (Fig. 3.19). Sulci on the internal aspect have a radial disposition, and enlargement of the occipital horn that maintains their fetal morphology, the so-called colpocephaly, is common (Noorani et al. 1988). Other abnormalities of the corpus callosum have been noted in a variety of neurodevelopmental conditions, e.g. hyperplasia of the corpus callosum, which may result from reduced postnatal axonal pruning. Dysgenesis of the corpus callosum refers to the corpus callosum being present but malformed in some way, including partial ACC and hypoplasia of the corpus callosum.

ACC can be an apparently isolated malformation, or be associated with additional cerebral malformations with potential detrimental effects on neurological function (complex ACC). Other associated abnormalities frequently include the formation of cysts dorsal to the third ventricle, communicating or noncommunicating (Griebel et al. 1995; Barkovich et al. 2001) cerebellar vermis and brainstem anomalies, and a miscellany of CNS malformations such as heterotopia, abnormalities of gyration or cephaloceles (Jeret et al. 1987; Barkovich and Norman 1988). Giant cysts may have a favourable outcome despite their impressive size (Haverkamp et al. 2002). CNS malformations were found in 33% of patients with complete and 42% of those with partial agenesis in one series (Bedeschi et al. 2006). It is these associated anomalies that are responsible for the clinical manifestations. Lipoma of the corpus callosum is almost invariably associated with agenesis of the structure (Zee et al. 1981; Vade and Horowitz 1992). Peripheral malformations are common. Eye abnormalities are especially frequent (Palmer and Mowat 2014).

It is recognised that genetic factors contribute to ACC in the vast majority of cases. Less commonly ACC can result from antenatal infections, vascular or toxic insults (Edwards et al. 2014; Palmer and Mowat 2014), and it is increasingly recognised that ACC, particularly isolated ACC, may be polygenic in many cases, due to an interaction of a number of ‘modifier’ genetic and environmental factors. All forms of genetic inheritance have been implicated, including X-linked, autosomal recessive and autosomal dominant. Chromosomal aberrations have been identified as an important cause and advanced maternal age is particularly associated with an increased prevalence of ACC due to chromosomal disorders (Glass et al. 2008). Callosal abnormalities can be associated with chromosomal trisomies (e.g. 13, 18 and mosaic trisomy 8), cytogenetically visible structural chromosomal rearrangements (e.g. 8p rearrangements), and an increasing number of submicroscopic copy number variants, detectable by chromosomal microarray. Twelve chromosomal loci are consistently associated with ACC and at least 30 other recurrent loci that may contain genes that cause or contribute to ACC (O’Driscoll et al. 2010; Edwards et al. 2014; Palmer and Mowat 2014) (Table 3.10).

Environmental factors include fetal alcohol syndrome. Several metabolic diseases, especially hyperglycaemia, pyruvate dehydrogenase deficiency, maternal phenylketonuria and other metabolic disorders collectively account for up to 2% of cases of callosal agenesis (Bamforth et al. 1988). Most cases are of unknown origin.

The clinical manifestations of callosal agenesis can be described under two different headings: nonsyndromic and syndromic forms (Davila-Gutierrez 2002). Nonsyndromic or isolated forms are the most common (Jeret et al. 1987; Serur et al. 1988). Neurodevelopmental outcome for individuals with isolated callosal abnormalities is very varied, even when the neuroanatomy appears relatively similar between patients. There is often significant overlap in neuropsychological outcome between patients with total and partial ACC, in that neuropsychological outcome is not clearly worse for patients with isolated total ACC compared to partial ACC. A recent integrative review highlighted that in truly isolated ACC (i.e. no additional neuroanatomical abnormalities identified on postnatal MRI) neurodevelopmental outcome for individuals diagnosed antenatally can range from essentially normal development, in about 75% of individuals, to differing levels of intellectual disability. About 12% of individuals in this series had severe intellectual disability (Sotiriadis and Makrydimas 2012).
Table 3.10  More common chromosomal aberrations associated with agenesis of the corpus callosum

<table>
<thead>
<tr>
<th>Chromosome abnormalities</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q42–q44 deletion</td>
<td>ACC of variable severity (high penetrance 80%) and postnatal microcephaly</td>
</tr>
<tr>
<td>4p16.3 deletion</td>
<td>Wolf–Hirschhorn syndrome [growth deficiency, variable developmental delay, congenital malformations (cardiac and renal), microcephaly, dysgenetic CC]</td>
</tr>
<tr>
<td>6q2 deletion</td>
<td>Periventricular nodular heterotopia, PMG, cerebellar malformations, hydrocephalus, ACC</td>
</tr>
<tr>
<td>8p rearrangements</td>
<td>Brain malformations including ACC</td>
</tr>
<tr>
<td>17q13.3 deletions</td>
<td>Lissencephaly +/- ACC, microcephaly, craniofacial dysmorphism</td>
</tr>
</tbody>
</table>

Adapted from O’Driscoll et al. (2010), Edwards et al. (2014) and Palmer and Mowat (2014).

ACC, agenesis of the corpus callosum; CC, corpus callosum; PMG polymicrogyria.

Several ACC syndromes are yet to have causative genetic mutations identified. Many of these syndromes are of interest because of the diversity of organ systems affected, which may allude to their underlying genetic aetiology (Edwards et al. 2014; Palmer and Mowat 2014) (Table 3.11).

**AICARDI SYNDROME**

Aicardi syndrome was classically characterised by a triad of features: agenesis of the corpus callosum, distinctive chorioretinal lacunae and infantile spasms (Aicardi 2005). However, it is now well recognised that several other important findings are typically present in girls with Aicardi syndrome. Neurological examination can reveal microcephaly, axial hypotonia and appendicular hypertonia with spasticity. Moderate to severe global developmental delay and intellectual disability are expected. Many girls with Aicardi syndrome develop seizures prior to age 3 months, and most before age 1 year. Ongoing medically refractory epilepsy with a variety of seizure types develops over time. Costovertebral defects are common and can lead to marked scoliosis in up to one-third of affected individuals. Other features include characteristic facial features, gastrointestinal difficulties, small hands, vascular malformations and pigmentary lesions of the skin, increased incidence of tumours, lower growth rate after ages 7–9 years, and precocious or delayed puberty. Survival is highly variable, with the mean age of death about 8.3 years and the median age of death about 18.5 years.

The diagnosis of Aicardi syndrome is based on clinical features including the pathognomonic chorioretinal lacunae (see Figure 1.28 in Chapter 1) identified on ophthalmological examination, brain MRI findings (Fig. 3.20) (dysgenesis of the corpus callosum, gross cerebral asymmetry with polymicrogyria or pachygria, periventricular and intracortical grey matter heterotopia, choroid plexus papillomas, ventriculomegaly and intracerebral cysts, often at the third ventricle and in the choroid plexus) and skeletal findings (hemivertebrae, block vertebrae, fused vertebrae and missing ribs). However, the spectrum of severity is wider than previously thought (Menezes et al. 1994). In rare cases, the corpus callosum may be present. Aicardi syndrome appears to be an X-linked dominant disorder with lethality in males, but no gene or candidate region on the X chromosome has been definitively identified. Pathologically, there are multiple areas of heterotopia and polymicrogyria of the unlayered type in the brain, while the so-called lacunae represent thinning of the pigment epithelium and choroid with loss of pigment granules (Billette de Villemeur et al. 1992). Ependymal cysts are frequently found around the third ventricle, and cysts or tumours of the choroid plexus may reach a large size (Aicardi 2005). They may permit prenatal diagnosis when found in association with callosal agenesis.

Other syndromic forms are rare or mostly restricted to certain ethnic groups. A familial syndrome of callosal agenesis with abnormal genitalia, which may also feature microcephaly and other CNS anomalies, is a part of the much larger spectrum of disorders associated with mutations in the ARX gene on chromosome Xp22.3 (Hartmann et al. 2004).
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical features</th>
<th>Genetics</th>
<th>Associated malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aicardi syndrome</td>
<td>Callosal agenesis infantile spasms (partial seizures), choroidoretinal lacunae and disc coloboma, severe DD vertebrocystal anomalies, 'split brain' EEG Ependymal cysts seen only in girls</td>
<td>XL dominant lethal in males</td>
<td>Periventricular heterotopia cysts of choroid plexus, other intracranial cysts, microgyria anomalies of posterior fossa</td>
</tr>
<tr>
<td>Shapiro syndrome</td>
<td>Spontaneous periodic hypothermia, excessive sweating (hyperhidrosis), agenesis of the corpus callosum</td>
<td>Non-familial</td>
<td>Hypothalamic lesion probably responsible for the syndrome that may occur with an intact callosum</td>
</tr>
<tr>
<td>Reverse Shapiro syndrome</td>
<td>Periodic hyperthermia, Callosal agenesis</td>
<td>Non-familial</td>
<td></td>
</tr>
<tr>
<td>Andermann syndrome</td>
<td>Neuropathy (mixed motor and sensory), peculiar facies, Callosal agenesis</td>
<td>Recessive mutations in SLC12A6</td>
<td></td>
</tr>
<tr>
<td>Acrocallosal syndrome</td>
<td>Corpus callosal agenesis +/-, Dandy–Walker malformation, dysmorphic features, postaxial polydactyly of the hands, preaxial polydactyly of the feet</td>
<td>Homozygous mutation in KIF7</td>
<td></td>
</tr>
<tr>
<td>X-linked lissencephaly with corpus callosum agenesis</td>
<td>Corpus callosal agenesis, hydranencephaly dysmorphism, ambiguous genitalia</td>
<td>Hemizygous mutation in ARX</td>
<td>Neonatal-onset epilepsy, hypothalamic dysfunction including deficient temperature regulation</td>
</tr>
<tr>
<td>Mowat Wilson</td>
<td>Microcephaly intellectual disability, epilepsy, characteristic facial features</td>
<td>De novo heterozygous mutation in ZEB2</td>
<td>Hirschsprung disease Congenital heart defects (47%), agenesis of the corpus callosum (35%), pre- or postnatal microcephaly, postnatal growth retardation</td>
</tr>
<tr>
<td>Oro-facio-digital syndrome</td>
<td>Cleft lip/palate, aplasia of the alar cartilages, lingual hamartomas, abnormal buccal frenula, digital malformations such as syndactyly or trident hand, intellectual disability limited to girls</td>
<td>XL dominant mutations in OFD1 (lethal in males)</td>
<td>Interhemispheric cysts, micropolgyria, dysplasia of cerebellum and the pons</td>
</tr>
<tr>
<td>Lissencephaly</td>
<td>See text</td>
<td>Dominant de novo tubulin mutations</td>
<td></td>
</tr>
<tr>
<td>Apert syndrome</td>
<td>Acrocephalosyndactyly craniostenosis, midface hypoplasia syndactyly of the hands and feet</td>
<td>Autosomal dominant mutation in the FGFR2 gene</td>
<td>Callosal agenesis, only occasional</td>
</tr>
<tr>
<td>Meckel–Gruber syndrome</td>
<td>Cystic renal disease, a central nervous system malformation, most commonly occipital encephalocele polydactyly, most often postaxial</td>
<td>Recessive mutation in MKS1 to 12 (genetic heterogeneity)</td>
<td>Callosal agenesis, only occasional</td>
</tr>
<tr>
<td>Goldenhar syndrome</td>
<td>Hemifacial microsomia unilateral deformity of the external ear, small ipsilateral half of the face with epibulbar dermoid vertebral anomalies, Coloboma of the upper eyelid</td>
<td>Autosomal dominant</td>
<td>Callosal agenesis, only occasional</td>
</tr>
</tbody>
</table>
ANDERMANN SYNDROME

Andermann syndrome was described in French Canadians in the Lake St John region (Larbrisseau et al. 1984) but a few cases have been reported outside Canada. The syndrome features involvement of the peripheral nervous system in addition to callosal agenesis or hypotrophy. Agenesis of the corpus callosum is often a part of oro-facio-digital syndrome type I.

Prenatal diagnosis is possible from 22 weeks (Bennett et al. 1996; Simon et al. 2000). Indirect ultrasound features that may indicate a corpus callosum anomaly include the absence of the cavum septi pellucidi, colpocephaly (dilatation of the atria and occipital horns of the lateral ventricles), abnormal course of the pericallosal artery, widening of the interhemisphere fissure and radial disposition of the sulci on the internal aspects of the hemispheres. The most common brain anomalies associated with corpus callosum include posterior fossa anomalies, interhemispheric cysts and neuronal migration disorders found in 45.8% of cases on a recent review (Sotiriadis and Makrydimas 2012). Fetal MRI is recommended as this allows direct visualisation of the corpus callosum and may identify additional brain abnormalities (Fig. 3.21).

The presence of additional ultrasound/MRI findings suggests a less favourable prognosis but a specific diagnosis is often not possible. Many couples elect to terminate the pregnancy in these circumstances. Many couples choose to terminate the pregnancy even in the absence of additional abnormal findings because of their concerns about a poor neurodevelopmental outcome. There is relatively little data looking at outcome in the context of isolated ACC and PACC although the emerging trend suggests a better outcome than previously expected. A recent review looked at the developmental outcome in 132 fetuses with isolated ACC from 16 studies and suggested that 71.2% have intelligence in the normal range, 13.6% have borderline or moderate disability and 15.2% have severe disability (Sotiriadis and Makrydimas 2012). In many of these cases the neurodevelopmental data, follow-up period and imaging modality varied widely. When limiting the analysis to isolated ACC, prenatal MRI and standardised neurodevelopmental assessment the rates were 75.4% and 11.6% for normal and severe disability, respectively (Sotiriadis and Makrydimas 2012). In a 10-year follow-up study of an original cohort of 17 children with antenatally detected isolated ACC, 27% had borderline intelligence and 73% were in the normal range (Moutard et al. 2012; D’Antonio et al. 2016).

SEPTO-OPTIC DYSPLASIA

Septo-optic dysplasia (SOD) is a rare disorder with postulated genetic and environmental aetiology, initially considered as a very rare disease with a reported incidence of 1 in 10 000, with equal sex distribution (Saracac and Gucev 2014). The diagnosis of SOD is predominantly a clinical one, and made with the presence of two or more features of the classic triad: (1) hypopituitarism, (2) optic nerve hypoplasia, and (3) midline brain defects, typically absence or hypoplasia of the septum pellucidum and/or corpus callosum (Fig. 3.22). Hypopituitarism ranges from isolated to multiple hormone deficits, with diabetes insipidus in a minority. The condition is heterogeneous.
and may also manifest additional brain defects. Although homozygous mutations in the homeobox gene HESX1 have been identified in SOD, these are uncommon and genetic diagnosis can be made in only less than 1% of patients with autosomal recessive inheritance. Autosomal dominant inheritance has also been reported. SOX2, SOX3 and OTX2 mutations have also been identified in some forms of SOD. The aetiology of SOD is uncertain but viral infections, environmental teratogens and vascular or degenerative damage have been postulated to account for its sporadic occurrence. Other factors (endogenous or exogenous) include parental age, parity, smoking, alcohol and substance abuse, antenatal haemorrhage and ethnicity. Cocaine abuse during pregnancy, which is a potent vasoconstrictor has recently been identified as a potential external cause. The phenotype of SOD is highly variable; the clinical picture may include visual impairment, short stature, obesity and sleep–wake inversion.

Approximately 75–80% of patients exhibit optic nerve hypoplasia, which may be the first presenting feature. The clinical features include variable degrees of visual disturbances. The optic discs have a characteristic appearance with a central part of less than half the normal diameter of the papilla, which represents the true disc, and a peripheral ring of about the size of a normal papilla. This double-contour is of great diagnostic value (Ouvrier and Billson 1986). Facial dysmorphism or endocrine abnormalities, especially growth hormone deficiency and diabetes insipidus, may occur (Masera et al. 1994) and should be searched for systematically in infants because they may produce hypoglycaemia with its complications and sequelae. Pituitary insufficiency may evolve over time, and children with possible SOD must be kept under careful endocrine follow-up.

Cases associated with other brain malformations have been termed ‘septo-optic dysplasia plus’ (Fitz 1994). Prenatal diagnosis of septal agenesis is possible (Leipnert et al. 2005) but isolated septal agenesis is difficult to differentiate from complex cases (Maling et al. 2005) and is only rarely encountered (Belhocine et al. 2005).

Other anomalies of the septum pellucidum include simple agenesis, cyst formation and persistence of the septum beyond the first year of life. Most are asymptomatic but they may be a marker for other brain malformations (Bodensteiner 1995). An occasional cyst may become symptomatic and compress the foramina of Monro with resulting hydrocephalus (Miki et al. 2005).

**MIDBRAIN–HINDBRAIN MALFORMATIONS**

The classification of midbrain–hindbrain (MBHB) malformations is based on embryologic, genetic, neuroimaging and pathophysiological information. It allows the distinction of four major groups of malformations (Jissendi-Tchofo et al. 2015).

1. Malformations secondary to early anteroposterior and doroventral patterning defects, or to misspecification of mid–hindbrain germinial zones.
2. Malformations associated with later generalised developmental disorders that significantly affect the brainstem and cerebellum (and have a pathogenesis that is at least partly understood).
3. Localised brain malformations that significantly affect the brainstem and cerebellum (pathogenesis partly or largely understood, includes local proliferation, migration and axonal guidance).
4. Combined hypoplasia and atrophy in putative prenatal onset degenerative disorders.

Little population-based data on the prevalence of MBHB malformations exists, due to the rarity of these disorders and substantial under-recognition on brain imaging studies. The postnatal prevalence of Dandy–Walker malformation has been estimated to be approximately 1 in 30 000 and 1 in 5000 (Parisi and Dobyns 2003). A prenatal prevalence of approximately 1 in 10 000 was estimated from a large birth defects registry in the United Kingdom (Doherty et al. 2013).

MBHB malformations are frequently diagnosed before birth. Prenatal ultrasound can identify cerebellar hypoplasia, abnormal fluid collections in the posterior fossa or poor delineation of posterior fossa landmarks. Fetal MRI allows a better definition of the malformation (Guibaud and des Portes 2006).

Postnatal presentation of patients with MBHB malformations is typically nonspecific features that include hypotonia, motor delay, and in some cases, characteristic cerebellar clinical syndrome with ataxia, dysmetry, nystagmus and oculomotor apraxia. More severely affected patients can present with...
apnoea, feeding and swallowing difficulties, spasticity, lack of developmental progress or seizures. Signs of cranial neuropathy, such as abnormal eye movements, ptosis, facial palsy, hearing impairment (with consequent speech delay) and facial/corneal anaesthesia, may also be observed. Ophthalmological evaluation may reveal chorioretinal coloboma or retinal dystrophy in a subset of patients with Joubert syndrome, a variety of structural eye abnormalities in patients with cobblestone malformations, or eye movement abnormalities. Cognitive impairment is common, but not universal, and autistic features are also observed. The range of neurodevelopmental outcome is broad. Mildly affected patients may have relatively isolated cranial nerve dysfunction, as in Duane retraction syndrome and horizontal gaze palsy with progressive scoliosis.

**PREDOMINANTLY CEREBELLAR MALFORMATIONS**

Cerebellar hypoplasia has many causes including chromosomal disorders, specific genetic syndromes and prenatal disruptions. They include the Dandy–Walker malformation and other types of dysgenesis of the cerebellar vermis, cerebellar aplasia or hypoplasia (Donkelaar et al. 2003) and rare anomalies such as rhombencephalosynapsis and tectocerebellar dysraphia. Chiari malformation has been described above.

**DANDY–WALKER MALFORMATION**

Dandy–Walker malformation (DWM) is perhaps the most common MBHB malformation. It is a heterogeneous disorder defined by a hypoplastic and commonly anticlockwise rotated vermis, an enlarged fourth ventricle, and an enlarged posterior fossa with an elevated torcular. Typically, the cerebellar hemispheres are less affected than the vermis, and the brainstem is normal to moderately hypoplastic. Subsets of patients have other brain findings such as ACC and hydrocephalus. DWM can be isolated, part of a defined syndrome or associated with extra-CNS malformations that do not fit with a known condition. Neuroimaging is characteristic (Fig. 3.23). In all cases, a huge collection is present that in half the cases extends upwards through the tentorial opening into the trigeminal cistern and/or downwards through the foramen magnum. It represents the greatly dilated fourth ventricle. The hemispheres are small but normal. The vermis is constantly small and rotated, pushed toward the tentorium. Sagittal cuts allow best visualisation of remnants of the vermis, which are pushed upwards toward the tentorium and anteriorly rotated. According to Klein et al. (2003), in most patients there are only two vermian fissures and three lobes; such patients have no associated malformation and their cognitive level is almost always within normal limits. In a smaller group, the vermis is malformed and presents only one or no fissure. These patients always have associated abnormalities and are likely to have severe intellectual disability (Boddaert et al. 2003; Klein et al. 2003). Prenatal diagnosis is relatively easy from the 18th to the 20th week.

Detailed evaluation of brain imaging is important to (1) distinguish DWM from more benign entities such as persistent Blake pouch cyst, in which a normal vermis is rotated anticlockwise by the cyst, and (2) identify mass-effect that might result in obstructive hydrocephalus.

The clinical manifestations of the Dandy–Walker syndrome are mainly those of hydrocephalus. Therefore, the diagnosis is made in 75% of cases after 3 months of age and often only by the first birthday, as hydrocephalus usually becomes apparent by 1 year of age. The head may be elongated in the anteroposterior direction, with bulging of the occiput, which may lead to fortuitous discovery of the anomaly. Remarkably, there are no cerebellar signs or disturbances of stance. Some degree of intellectual disability is present in 30–50% of patients and may be the reason for radiological examination (Boddaert et al. 2003).

Treatment involves shunting the hydrocephalus rather than opening the cystic fourth ventricle. Some surgeons advise inserting the shunt into the fourth ventricle but this is not a unanimous opinion. Additional shunting of the trapped fourth ventricle may be necessary when the lateral ventricles have been shunted. Endoscopic surgery can give good results (Mohanty et al. 2006).

The mechanism of Dandy–Walker syndrome was formerly thought to be atresia of the foramina of Magendie and Luschka. However, it is neither constant nor characteristic.
It in 2009, mutations of FOXC1 (Forkhead box C1, mapped to locus 6p25 OMIM 601090), a gene that is expressed in the developing leptomeninges but not in the brain, in humans were identified to cause posterior fossa abnormalities ranging from hypoplasia of the vermis or entire cerebellum, with or without enlarged fourth ventricle, to mega cisterna magna, all included in the Dandy–Walker spectrum (Aldinger et al. 2009). Precisely how mutations in the leptomeninges cause hypoplasia of underlying parenchyma is not fully established. Therefore, the earlier concept of hindbrain cystic malformations, being a combination of abnormalities including variable increase of the posterior fossa size and cerebrospinal fluid volume (mesenchymal anomalies) on the one hand and variably impaired growth of the cerebellum (neuroectodermal anomalies) on the other hand, seem to be reasonable in light of new genetic mechanisms as mentioned above.

**CEREBELLAR INVOLVEMENT IN MIGRATIONAL DISORDERS**

Cerebellar hypoplasia may be found in patients with cerebral malformations in the lissencephaly spectrum, caused by defects in the RELN pathway or microtubule function. Reported patients with RELN mutations have pachygryria and minimal foliation of a very hypoplastic cerebellum, vermis worse than hemispheres (Hong et al. 2000) (Fig. 3.11). Profound developmental disability, microcephaly, sloping forehead, seizures and congenital lymphedema have also been reported in these patients. In contrast, patients with mutations in VLDLR have a simplified, mildly pachygyric cerebral cortex and milder cerebellar hypoplasia with some degree of cerebellar foliation (Ozcelik et al. 2008).

Similarly, in tubulinopathies are caused by mutations in TUBA1A, TUBA8, TUBB2B, TUBB3 and TUBB5 genes, cerebellar hypoplasia is common. Clinical features range from isolated congenital fibrosis of the extracerebral muscles to severe intellectual disability, quadriplegic cerebral palsy, seizures, cranial neuropathies and hydrocephalus. Neuroimaging features include cortical dysgenesis (lissencephaly or polymicrogyria), malformation of cranial nerves and basal ganglia, often with cerebellar and pontine hypoplasia, as well as defects in the corpus callosum, anterior commissure and internal capsule (Fig. 3.10). While most occurrences are sporadic and due to de novo mutations, recurrences have been reported due to germline mosaicism and autosomal recessive inheritance (Bahi-Buisson and Cavallin 1993; Bahi-Buisson et al. 2014; Mutch et al. 2015).

Finally, cerebellar dysplasia with cysts (CDC) is an imaging finding typically seen in combination with cobblestone cortex and congenital muscular dystrophy in individuals with dystroglycanopathies. Similarly, cerebellar dysplasia with cysts are also common in GPR56 related fronto parietal polymicrogyria. More recently, CDC was reported in patients without neuromuscular involvement (Poretti-Boltshauser syndrome), caused but LAMA1 mutations (Aldinger et al. 2014).

**CEREBELLAR AGEnESIS**

Cerebellar agenesis is an extremely rare condition characterised by near-complete absence of the cerebellum (Bosemani and Poretti 2016). Cerebellar agenesis is defined on the basis of the morphological pattern/neuroimaging findings and does not suggest the pathogenesis. In cerebellar agenesis, the cerebellar tissue is usually not completely absent; remnants of the anterior vermal lobules, flocculus and/or middle cerebellar peduncles may remain. The volume of the posterior fossa is variable, mostly of normal or increased size. Secondary brainstem involvement, with marked pontine hypoplasia and absence of the protuberance of the inferior olives is typically seen.

Cerebellar agenesis appears to result from at least two distinct pathophysiological mechanisms. First is a genetically mediated condition presenting as a primary malformation (e.g. mutations in PTF1A) (Sellick et al. 2004). The other is a secondary/acquired disruption resulting from: (1) pre- or perinatal haemorrhage; (2) vascular insufficiency/compromise in Chiari II malformation with cerebellar herniation; and (3) as a sequela of preterm birth.

Almost all children with cerebellar agenesis are symptomatic. However, the clinical presentation of cerebellar agenesis appears to be quite heterogeneous, ranging from early death in presumed genetically mediated complex cerebellar agenesis to variable degrees of cerebellar dysfunction, including cognitive impairment in cases of isolated cerebellar agenesis following disruption. Motor dysfunction in patients with cerebellar agenesis is characterised by truncal ataxia, limb ataxia with dysmetria, intention tremor, dysarthria and lower extremity spasticity. Dexterity was studied in one adult with cerebellar agenesis who generated greater grasping forces compared to healthy controls, and who showed impairment of the predictive adjustment of grasping forces to the differential loading requirements of movement direction. Ocular motor abnormalities include strabismus and nystagmus (gaze-evoked and periodic alternation nystagmus), saccadic intrusions into smooth pursuit eye movements in three, hypometric saccades.

**OTHER CEREBELLAR HYPOPLASIAS**

While the cause of cerebellar hypoplasia remains unknown in many patients, a number of other rare cerebellar hypoplasia syndromes have been identified. Cerebellar hypoplasia, ventriculomegaly, intellectual disability, seizures and mildly dysmorphic facial features are characteristic in males and occasionally in females with mutations in the X-linked OPHN1 gene (Billuart et al. 1998; des Portes et al. 2004; Zanni et al. 2005).

PHACE syndrome is characterised by posterior fossa brain malformations, hemangioma of the head and/or neck, arterial lesions of the head and/or neck, cardiac defects including aortic coarctation and eye abnormalities (Garzon et al. 2016).
Unilateral cerebellar hypoplasia, ipsilateral to the hemangioma and cerebrovascular lesions are the most common brain imaging findings with occasional cerebellar vermis and supratentorial malformations (corpus callosum dysgenesis, polymicrogyria and heterotopia) (Oza et al. 2008).

**RHOMBENCEPHALOSYNAPSIS**

Rhombencephalosynapsis consists of partial or complete absence of the cerebellar vermis with continuity of the hemispheres across the midline, thought to be due to aberrant dorsal–ventral patterning. The severity of rhombencephalosynapsis on MRI correlates with clinical outcome (Ishak et al. 2012). When severe, the fused cerebellar nuclei arch in a horseshoe shape across the midline, with a narrow fourth ventricle; the primary and pyramidal fissures of the vermis cannot be identified. Rhombencephalosynapsis is often associated with midbrain abnormalities, i.e. aqueductal stenosis and midline fusion of the colliculi, and supratentorial abnormalities such as absent septum pellucidum and corpus callosum dysmorphisms.

Affected patients can be divided into at least three recognisable categories:

1. Gómez-López-Hernández syndrome combining rhombencephalosynapsis with scalp alopecia and trigeminal anaesthesia,
2. Rhombencephalosynapsis plus features of VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal defects and limb defects, and
3. Rhombencephalosynapsis with atypical holoprosencephaly, most severely affecting the occipital lobes.

Developmental outcomes vary widely; patients with isolated rhombencephalosynapsis can function independently in adulthood, while patients with VACTERL features or holoprosencephaly are more likely to manifest significant impairments. No genetic defects have been linked to rhombencephalosynapsis.

**CEREBELLAR HYPERPLASIA OR MACROCEREBELLUM**

Cerebellar hyperplasia is a rare neuroimaging finding that can be seen in isolation, or in a variety of disorders including chromosomal abnormalities, Alexander disease and fucosidosis, as well as Sotos, Williams, Costello, MCAP/MPPH syndromes (Doherty et al. 2013). While the developmental mechanisms underlying cerebellar hyperplasia in most of these disorders remains unknown, substantial progress has been made in the understanding of brain overgrowth in MCAP/MPPH. MCAP/MPPH are typically diagnosed due to supratentorial overgrowth and polymicrogyria (Mirzaa and Poduri 2014). Although cerebellar size is normal at birth, many patients develop macrocerebellum with normal posterior fossa size, resulting in cerebellar ectopia/Chiari I malformation and associated symptoms (posterior headache, dysphagia, stridor) and hydrocephalus.

Most patients have pathway activating de novo mutations in components of the PI3K-AKT-mTOR pathway that result in increased cell growth (Riviere et al. 2012).

**CEREBELLAR DYSPLASIA**

Any part of the cerebellum can be dysplastic, from small focal portions of a single hemisphere to abnormal foliation of the entire cerebellum (Demaerel 2002) (Fig. 3.24). Very often, such as in Joubert syndrome and cobblestone malformations, the hypoplastic cerebellum is also dysmorphic. Outside of these conditions, little is known about the causes of cerebellar cortical dysgenesis. One exception is Chudley-McCullough syndrome, in which patients have striking disorganisation of the inferior cerebellar hemisphere folia. Clinically, these patients present with severe sensorineural hearing loss and mild delays, but are not usually dysmorphic and do not have other malformations. Brain imaging reveals additional abnormalities including frontal polymicrogyria with subcortical heterotopia, corpus callosum hypogenesis and arachnoid cysts. All patients to date have biallelic truncating mutations in the GPSM2 gene that encodes a GTPase regulator required for correct orientation of stem cell divisions in multiple tissues (Doherty et al. 2012). It is likely that aberrant cell division underlies the cerebellar dysplasia, but the mechanism remains unknown.

**OTHER UNUSUAL CEREBELLAR MALFORMATIONS**

Tectocerebellar dysraphia (Dehdashti et al. 2004) is a complex anomaly that includes an inverted cerebellum developed inside the fourth ventricle, hypoplasia of the vermis and occipital cephalocele. Of note, there is evidence that at least in some of the patients, tectocerebellar dysraphism is a morphological pattern within the spectrum of Joubert syndrome (Poretti et al. 2011).

Dentato-olivary dysplasia is a very rare cerebellar malformation characterised by a particular form of the inferior
olives which are hook shaped, coarse, and lacking undulations. It is responsible for neonatal tonic seizures reminiscent of Ohtahara syndrome has been found in a few patients. A genetic origin is likely (Barth 2011).

CEREBELLAR AND BRAINSTEM MALFORMATIONS

PONTOCEREBELLAR HYPOPLASIA

Pontocerebellar hypoplasia occurs in a number of disorders that can be distinguished, in part, by neuroimaging findings and associated features.

To date, 10 subtypes of pontocerebellar hypoplasia with different phenotypes and pathogeneses (types 3 and 8 have a non-progressive course) have been identified (Bosemani et al. 2015; Bosemani and Poretti 2016). Pontocerebellar hypoplasia type 1, associated with mutations in EXOSC3 (Wan et al. 2012) and VRK1 (Renbaum 2009), is characterised by moderate pontocerebellar hypoplasia on MRI in combination with spinal muscular atrophy, resulting in substantial global weakness and decreased or absent reflexes. Pontocerebellar hypoplasia types 2, 4 and 5 are now known to be caused predominantly by mutations in genes that encode tRNA splicing endonucleases (TSEN54, TSEN34 and TSEN2) (Rudnik-Schoneborn et al. 2014; Namavar et al. 2011). Patients with pontocerebellar hypoplasia type 2 represent the less severe end of the spectrum with early hyperreflexia, developmental delay and feeding problems, eventually developing spasticity and involuntary movements in childhood, while patients with pontocerebellar hypoplasia type 4 represent the severe end of the spectrum characterised by polyhydramnios, severe hyperreflexia, contractures and early death due to central respiratory failure. Microcephaly is present at birth in patients with pontocerebellar hypoplasia type 4, while microcephaly develops over time in pontocerebellar hypoplasia type 2. Seizures are common in both groups. A typical feature of TSEN-related pontocerebellar hypoplasia is more severe involvement of the cerebellar hemispheres compared to the vermis, with the so-called ‘dragonfly aspect’ (Fig. 3.25). It is noteworthy that this aspect may be seen in preterm infants with disruptive cerebellar development (Poretti et al. 2014).

Pontocerebellar hypoplasia type 3 is associated with optic atrophy and caused by mutations in PCLO gene (Ahmed et al. 2015). Pontocerebellar hypoplasia type 6 is associated with elevated cerebrospinal fluid lactate and caused by mutations in the RARS2 gene (Edvardson et al. 2007).

Other disorders can mimic the TSEN-related pontocerebellar hypoplasias. The severe end of the spectrum of CASK-related disease also presents with progressive microcephaly and pontocerebellar hypoplasia that proportionately affects the vermis and hemispheres (Fig. 3.26) (Najm et al. 2008). The CASK gene is on the X chromosome, so CASK-related pontocerebellar hypoplasia is more common in females, presumably due to lethality in males. Most recently, recessive loss of function mutations in CHMP1A have been shown to cause severe pontocerebellar hypoplasia with proportionate involvement of the cerebellar vermis and hemispheres and preserved foliation pattern (Najm et al. 2008). Described patients
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had moderate to severe developmental delay, acquired microcephaly, increased extremity tone and contractures.

Pontine tegmental cap dysplasia is characterised by multiple cranial neuropathies, particularly hearing loss, trigeminal anaesthesia, facial paralysis and swallowing dysfunction (Barth et al. 2007). Pontine tegmental cap dysplasia can be distinguished from other pontocerebellar hypoplasias by the characteristic ‘cap’ of tissue on the dorsal pons and severe hypoplasia of the inferior and middle cerebellar peduncles (Fig. 3.27). Congenital heart, kidney, vertebral and rib defects are present in subsets of patients. Developmental disability is typically severe, and the degree of impairment may correlate with the severity of brainstem dysplasia, with mildly affected patients having a rounded bump (‘cap’) and those more severely affected having a more angular brainstem kink (‘beak’). Neither familial recurrence nor genetic causes have been reported.

Hypoplasia of the pons and cerebellum with progressive volume loss is characteristic of congenital disorders of glycosylation type 1a (Fig. 3.28) (Feraco et al. 2012). Patients present with hypotonia and developmental delay, but can also display a striking variety of other features including abnormal fat distribution, coagulopathy, retinal degeneration, peripheral neuropathy, stroke-like episodes and seizures. The range of developmental outcome is broad. This disorder is autosomal recessive, caused by biallelic mutations in the PMM2 gene, required for N-glycosylation of proteins (Matthijs et al. 1997).

Many causes of pontocerebellar hypoplasia remain undefined, although atypical presentations of disorders such as VLDLR-related disequilibrium syndrome (Ozcelik et al. 2008) or pre- and postnatal insults (most commonly complications of extreme preterm birth) may explain additional subsets of patients.

**JOUBERT SYNDROME/MOLAR TOOTH MALFORMATION**

Joubert syndrome is a congenital cerebellar ataxia with autosomal recessive or X-linked inheritance, the diagnostic hallmark of which is a unique cerebellar and brainstem malformation recognisable on brain imaging the so-called molar tooth sign. Neurological signs are present from the neonatal period and include hypotonia progressing to ataxia, global developmental delay, ocular motor apraxia, and breathing dysregulation (Valente et al. 2005). These signs are variably associated with multi-organ involvement, mainly of retinal dystrophy, nephronophthisis, liver fibrosis and polydactyly (Romani et al. 2013). The outcome is variable. Intellectual disability is the rule but is of variable degree (Hodgkins et al. 2004). A normal intelligence may be preserved in some cases. Supportive treatment and physiotherapy and appropriate education are always justified.

Brain MRI is usually diagnostic, revealing cerebellar vermis hypoplasia/dysplasia, long, thick, elevated superior cerebellar peduncles and a thin MBH junction with a deep interpeduncular fossa resulting in the ‘molar tooth sign’ on axial MRI (Fig. 3.29 and Fig. 1.15 in Chapter 1). The spectrum of associated findings in Joubert syndrome is wide. Other brain malformations can be present, including polymicrogyria, brainstem and cortical heterotopia, agenesis of the corpus callosum and/or cephalocele (Poretti et al. 2011).

Diagnosing Joubert syndrome is important, since it is recessive and carries a 25% recurrence risk. In addition,
close monitoring for the progressive retinal, kidney and liver disease is required to reduce complications. Mutations in more than 35 genes can cause Joubert syndrome and related disorders. The gene products function in the primary cilium–centrosome complex making these disorders part of an expanding group of disorders called ‘ciliopathies’ (Hildebrandt et al. 2011; Poretti et al. 2017). Remarkably, neuroimaging does not predict the genetic cause, but may predict the neurodevelopmental outcome. A high degree of vermis hypoplasia correlates with worse neurodevelopmental outcome. This finding is important for prognostic counselling in Joubert syndrome.

Figure 3.29 Joubert syndrome related to NPHP8 mutation in a 24-year-old man. Note the typical aspect of molar tooth with superior vermian dysplasia and thick cerebellar peduncles and partial agenesis with dysplasia of the vermis. Cerebellar hemispheres are normal.

PREDOMINANTLY BRAINSTEM MALFORMATIONS

CONGENITAL CRANIAL DYSINNERVATION DISORDERS

The term congenital cranial dysinnervation disorders refer to abnormalities of cranial nerve development that result in abnormal movement of the face and eyes, (Gutowski et al. 2003) most of which do not have obvious brainstem abnormalities on clinical MRI studies. The exception is horizontal gaze palsy with progressive scoliosis (HGPPS; OMIM 617313), an autosomal recessive disorder associated with a ‘butterfly shaped pons and medulla’ (Jen et al. 2004). Patients typically present with progressive scoliosis during early childhood and congenital eye movement abnormalities and defects in midline axon crossing demonstrated by somatosensory and motor evoked potentials. HGPPS is due to biallelic mutations in ROBO3 which encodes a receptor required for axon guidance (Jen et al. 2004).

PREDOMINANTLY MIDBRAIN MALFORMATIONS

Relatively few disorders that predominantly affect the midbrain have been described (Doherty et al. 2013). Of these, the diencephalic–mesencephalic junction dysplasia has been described as a novel recessive brain malformation in several consanguineous Egyptian families (Zaki et al. 2012). On neuroimaging, the patients had rostral–caudal shortening and dorsal–ventral lengthening of the midbrain, with a deep interpeduncular cistern. In two patients, the corticospinal tracks were not detectable at the level of the pons by diffusion tensor imaging. Variable features included cortical calcifications, agenesis of the corpus callosum, ventriculomegaly, brainstem dysplasia and cerebellar vermis hypoplasia. Clinically, the patients had progressive microcephaly, spasticity, intellectual disability and seizures. Inheritance appeared to be autosomal recessive, but the genetic cause(s) remains unknown.

PREGNATAL DIAGNOSIS, TREATMENT AND PREVENTION OF BRAIN MALFORMATIONS

The possibilities for active treatment of brain malformations are limited. Those malformations that induce hydrocephalus can be effectively managed by ventriculo-peritoneal shunt or other shunting operations. Even in such cases, however, neurodevelopmental dysfunction may persist after successful operation because diffuse abnormalities are present in addition to hydrocephalus. The drug treatment of epilepsy has significantly progressed over the past decades, and surgery, especially for epileptogenic dysplasias (Chapter 16), has become a practical possibility in some cases and will continue to develop, being as yet under-utilised. For many patients, however, rehabilitation and physiotherapy are the major tools. Special education is needed in many cases, and for the most the most severely affected children may require care in an institution.
Prevention of CNS malformations is one of the major challenges for child neurology in the coming years. In the present state of knowledge, primary prevention is feasible for neural tube defects by administration of folic acid. Short of primary prevention, genetic counselling and prenatal diagnosis are the major preventive means available.

Genetic counselling requires that a precise diagnosis of fixed encephalopathies is made and that the rules of inheritance of the various types are known (Lie et al. 1994). Major advances in neuroimaging (Garel 2004; Gressens and Luton 2004) especially fetal MRI, have permitted visualisation of important malformation syndromes like polymicrogyria and some ‘minor’ malformations that were very difficult or impossible to diagnose previously. Ideally, a diagnosis of CNS malformation should be not only precise but early if genetic counselling is to be effective.

Prenatal diagnosis of several brain malformations is feasible mainly by ultrasonography (Aubry et al. 2003; Barnewolt and Estroff 2004). Improvement in techniques makes earlier and firmer recognition of many malformations possible. Fetal MRI is currently available in major centres and allows a more precise definition of the pathological features of the malformations (Garel 2004; Golja et al. 2004; Gressens and Luton 2004). It is indicated when sonographic diagnosis is uncertain or additional anatomical precision is required. With technical progress the diagnosis has become possible earlier in many conditions, but in others remains relatively late, with the consequence that only late termination is possible, which compares unfavourably with the earlier diagnosis of cases of metabolic diseases. Additionally, the reliability of ultrasonography depends heavily on the skill of examiners. A difficult ethical issue may be raised by some abnormalities such as the

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<td>Abnormal gyration</td>
<td>Okumura et al. (2008)</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase complex deficiency</td>
<td>Migration disorder</td>
<td>Samson et al. (1994), Lincke et al. (1996), Del Giudice et al. (2000)</td>
</tr>
<tr>
<td>Leigh disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory chain disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol metabolism disorders</td>
<td>Microcephaly, abnormal gyration, holoprosencephaly</td>
<td>Tint et al. (1994), Nissenkorn et al. (2001)</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>Pontocerebellar hypoplasia</td>
<td>Jaeken and Carchon (1993)</td>
</tr>
<tr>
<td>Glycoprotein disorders, carbohydrate-deficient glycoprotein (CDG) syndrome</td>
<td>Vermis hypoplasia</td>
<td>Jaeken and Van den Berghe (1984)</td>
</tr>
<tr>
<td>Adenylosuccinase deficiency Sphingosidoses</td>
<td>Corpus callosum agenesis</td>
<td>Two personal cases</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td>Agenesis of corpus callosum</td>
<td>Jellinger et al. (1981)</td>
</tr>
<tr>
<td>Hunter disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic disturbances</td>
<td>Microcephaly, callosal agenesis</td>
<td>Rouse et al. (2000)</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>Holoprosencephaly, sacral agenesis, septo-optic dysplasia</td>
<td>Anderson et al. (2005)</td>
</tr>
</tbody>
</table>

Prevention of CNS malformations is one of the major challenges for child neurology in the coming years. In the present state of knowledge, primary prevention is feasible for neural tube defects by administration of folic acid. Short of primary prevention, genetic counselling and prenatal diagnosis are the major preventive means available.

Genetic counselling requires that a precise diagnosis of fixed encephalopathies is made and that the rules of inheritance of the various types are known (Lie et al. 1994). Major advances in neuroimaging (Garel 2004; Gressens and Luton 2004) especially fetal MRI, have permitted visualisation of important malformation syndromes like polymicrogyria and some ‘minor’ malformations that were very difficult or impossible to diagnose previously. Ideally, a diagnosis of CNS malformation should be not only precise but early if genetic counselling is to be effective.

Prenatal diagnosis of several brain malformations is feasible mainly by ultrasonography (Aubry et al. 2003; Barnewolt and Estroff 2004). Improvement in techniques makes earlier and firmer recognition of many malformations possible. Fetal MRI is currently available in major centres and allows a more precise definition of the pathological features of the malformations (Garel 2004; Golja et al. 2004; Gressens and Luton 2004). It is indicated when sonographic diagnosis is uncertain or additional anatomical precision is required. With technical progress the diagnosis has become possible earlier in many conditions, but in others remains relatively late, with the consequence that only late termination is possible, which compares unfavourably with the earlier diagnosis of cases of metabolic diseases. Additionally, the reliability of ultrasonography depends heavily on the skill of examiners. A difficult ethical issue may be raised by some abnormalities such as the

Table 3.12 Central nervous system malformations that may be associated with metabolic disorders

<table>
<thead>
<tr>
<th>Metabolic disorder</th>
<th>Malformation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxisomal disorders</td>
<td>Cortical migration disorders, pachygyria and microgyria</td>
<td>Powers (1995)</td>
</tr>
<tr>
<td>Zellweger syndrome, neonatal adrenoleukodystrophy</td>
<td>Cerebellar atrophy</td>
<td>Christensen et al. (1990)</td>
</tr>
<tr>
<td>Trihydroxycholastanaemia</td>
<td>Agensis of corpus callosum</td>
<td>Nissenkorn et al. (2001)</td>
</tr>
<tr>
<td>Organic acid disorders</td>
<td>Macrocephaly, pseudo-cysts of temporal lobes</td>
<td>Martinez-Lage et al. (1994)</td>
</tr>
<tr>
<td>Glutaric aciduria type I</td>
<td>Status verrucosus of cortex, vermal agenesis</td>
<td>Takanashi et al. (1999)</td>
</tr>
<tr>
<td>Glutaric aciduria type II</td>
<td>Agenesis of corpus callosum</td>
<td>Nissenkorn et al. (2001)</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>Abnormal gyration</td>
<td>Okumura et al. (2008)</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase complex deficiency</td>
<td>Migration disorder</td>
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<td>Anderson et al. (2005)</td>
</tr>
</tbody>
</table>
Dandy–Walker syndrome or agenesis of the corpus callosum as these may be unassociated with neurodevelopmental dysfunction in a significant proportion of cases.

For the diagnosis of chromosomal abnormalities, spina bifida and some metabolic disorders, amniocentesis or chorionic villus sampling may be required. These techniques are associated with a risk of fetal loss of approximately 0.5–1% for amniocentesis performed under ultrasound guidance (Seeds 2004) and of 3% for villus sampling (Caughhey et al. 2006). The risk of of puncture injury of the fetus is very small but does exist (Seeds 2004).

Several developmental CNS anomalies may be associated with metabolic diseases. Some of these can be prevented by the control of the metabolic abnormality in the mother (e.g. phenylketonuria or diabetes) or by prevention of toxic effects of certain drugs or other toxic substances like alcohol, and several can be detected prenatally (Table 3.12). Several inborn errors of metabolism are a cause of CNS malformations (Nissenkorn et al. 2001). Nonketotic hyperglycaemia, mitochondrial and peroxisomal disorders have been repeatedly indicted.

Metabolic disturbances of environmental origin, whether due to maternal disease or to use of toxic substances during pregnancy, are a significant cause of fetal malformations. Maternal diabetes mellitus (Anderson et al. 2005) is one major metabolic disorder capable of increasing considerably the incidence of certain CNS malformations, especially holoprosencephaly. Moreover, the clear correlation that exists between high levels of glycosylated haemoglobin A1 in early pregnancy and the occurrence of severe defects in offspring supports the hypothesis that malformations in infants of diabetic mothers occur early during the first 7 weeks of gestation. Such findings indicate that strict control of maternal diabetes is essential. Maternal phenylketonuria is another cause of central nervous system malformations.

Maternal alcoholism is an important factor. Fetal effects including CNS malformations have been extensively reviewed and publicised, and the use of any quantity of alcohol during pregnancy will miss a significant number of brain malformations whatever the technique used.

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Neurocutaneous Diseases and Syndromes

Eleni Panagiotakaki and Alexis Arzimanoglou

Several diseases affect both the skin and the nervous system, which is probably a consequence of their common ectodermal origin. Most of these disorders are genetically determined and manifest early in life, although late manifestations are frequent as many of the neurocutaneous syndromes are evolutive conditions.

The group of the neurocutaneous disorders is highly heterogeneous and includes conditions completely unrelated pathophysiologically. They are studied together only because they feature clinically both cutaneous and neurological symptoms and signs, however different these can be. The term 'phakomatosis' is still sometimes used as a synonym. However, it has come to be applied mainly to those neurocutaneous diseases in which an excessive growth potential, with frequent development of hamartomas or tumours, is present. This applies to neurofibromatosis, tuberous sclerosis, von Hippel–Lindau disease and some other conditions with a proliferative tendency such as Proteus syndrome or nevoid basal cell carcinoma syndrome. In this chapter, the term neurocutaneous syndrome is used for all diseases in which there is a nonfutitious association of skin and nervous system abnormalities, including those in which the nervous system involvement consists of vascular abnormalities, even though the cutaneous manifestations may not be regularly present in all patients. The grouping used is clearly arbitrary, but it is justified from a clinical point of view as the association of cutaneous and neurological manifestations raises specific problems. Neurocutaneous diseases are much more pleiotropic than suggested by their name as they may involve viscera as well as skin and the central nervous system (CNS). Most neurocutaneous diseases are genetically determined; all three major Mendelian types of inheritance being possible. Sporadic syndromes may be due to somatic mutations or to other, unknown mechanisms.

Although the group of neurocutaneous diseases is heterogeneous, new concepts such as toropathies bring together diseases considered until now as non-related. The term refers to the tuberous sclerosis complex (TSC) disorders (due to mutations in the TSC1 or TSC2 genes), Cowden syndrome (mutations in PTEN) and neurofibromatosis type 1 (neurofibromin 1 mutations). The mammalian target of rapamycin (mTOR) signalling pathway regulates cell growth and differentiation. Loss-of-function mutations in upstream regulators of mTOR give rise to dysplasias, epileptic seizures and neurodevelopmental disorders (Galanopoulou et al. 2012).

NEUROFIBROMATOSIS

Neurofibromatosis is not a single disorder and includes a spectrum of disorders that share many features but clearly differ from one another; there is no agreement as to how many entities belong to the neurofibromatoses. Two distinct forms are generally recognised: Type 1 (NF1), also termed von Recklinghausen disease or peripheral type; and Type 2 (NF2), also termed central neurofibromatosis. These two types are distinct diseases genetically and clinically. The gene of NF1 is located in the pericentric region of the long arm of chromosome 17 (17q11.2), while that of NF2 is on the long arm of chromosome 22 (22q11.2). Both genes act as tumour suppressor genes.

The NF1 gene codes for a protein, neurofibromin, that appears to be a GTPase-activated protein. GTPase converts the proto-oncogen p21-ras from active to inactive form, thus downregulating the production of oncogen and having a probable anti-oncogenic function (De Luca et al. 2005). Most patients with NF1 and intellectual disability are associated with large deletions of the gene.

The NF2 gene codes for merlin, a cytoskeletal-membrane linking protein with roles in the suppression of growth-associated signalling pathways (Hamaratoglu et al. 2006; Plotkin et al. 2014). Interestingly, a loss of chromosome 22, and hence of the NF2 gene, is commonly found in schwannomas and meningiomas that occur outside NF2.

Other types of neurofibromatosis exist. Riccardi (1992) has proposed that seven distinct forms may be recognised. However, the individualisation of some of these forms remains
controversial. The terms central and peripheral are better abandoned because both NF1 and NF2 produce CNS lesions, albeit of different types. The diagnosis of patients with neurofibromatosis is essentially clinical and is usually easy. Table 4.1 shows the criteria for the diagnosis of NF1 and NF2. The basic disturbance in neurofibromatosis appears to be an abnormality in development of the neural crest cells with resulting tendency to abnormal, excessive growth of affected tissues and the development of multiple tumours.

**NEUROFIBROMATOSIS TYPE 1**

Neurofibromatosis Type 1 (NF1) accounts for at least 85% of all cases of neurofibromatosis. The prevalence of the disease is about 1 in 3000 individuals. NF1 is inherited dominantly with a 98% penetrance but with a high degree of phenotypic variability. According to Huson et al. (1988) and North (1993), approximately half of people with NF1 have only minor manifestations. Paternal transmission is more common than maternal inheritance. Occasional occurrence of a paternal germ line mosaic may account for the rare occurrence of more than one affected offspring of clinically unaffected parents (Lázaro et al. 1994). About one-third of cases involve new mutations, and the mutation rate is approximately one mutation per 10 000 gametes per generation.

**Cutaneous Manifestations of NF1**

Skin features of NF1 consist of abnormalities of pigmentation and tumours (Fig. 4.1). Café-au-lait spots are the hallmark of NF1 and are found in virtually all patients. Their size varies with age; they often are absent at birth but are present from an early age, although they are not as readily visible in infancy as they are later. Ordinarily, at least six spots 0.5–1.0 cm are apparent by 1 year of age but an occasional patient may have less. Of 46 children with such spots prospectively followed by Korf (1992), 27 had developed other signs of NF1 (in the majority, within 3 years), six had segmental neurofibromatosis, three received other diagnoses and eight remained without diagnosis. Axillary freckling was present in 84% of 200 children followed by North (1993), and inguinal freckling was found in about half these patients. Diffuse pigmentation may overlie a plexiform neuroma. Xanthomas and angiomas are less common features. Neurofibromas may be intracutaneous and are then of a violaceous colour and a soft consistency, or subcutaneous and presenting as firm tumours along the trunk of peripheral nerves. They vary from a few millimetres to 3–4 cm at their greatest diameter. Neurofibromas are sometimes found in children under 10 years old, but they increase steadily in number with age, especially around puberty (Riccardi 1992). They can lead to peripheral neuropathy when they affect larger nerves.

**Table 4.1 Criteria for the diagnosis of the neurofibromatoses**

<table>
<thead>
<tr>
<th>Neurofibromatosis type 1 (NF1)</th>
<th>If present at or before the age of 30 years</th>
<th>If present after the age of 30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Six or more café-au-lait spots &gt;5 mm in diameter in prepubertal patients and &gt;15 mm in postpubertal patients</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2. Two or more neurofibromas (intracutaneous or subcutaneous) or one plexiform neurofibroma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Freckling in the axillary or inguinal region</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4. Optic glioma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Two or more iris hamartomas (Lisch nodules)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6. Typical osseous lesion such as sphenoid dysplasia or talib pseudarthrosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7. One or more first-degree relative/s with NF1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

NF1 may be diagnosed if two or more of above criteria are present.

<table>
<thead>
<tr>
<th>Neurofibromatosis type 2 (NF2)*</th>
<th>If present at or before the age of 30 years</th>
<th>If present after the age of 30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. First-degree relative with NF2 diagnosed by these criteria</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2. Unilateral vestibular schwannoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. Second vestibular schwannoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. One meningioma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Second meningioma (no additional points for more than two meningiomas)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>6. Cutaneous schwannoma (one or more)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7. Cranial nerve tumor (excluding vestibular schwannoma) (one or more)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8. Mononeuropathy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>9. Cataract (one or more)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Modified from National Institutes of Health Consensus Development Conference (1988). Using these criteria a definite diagnosis can be made in 94% of patients. *The patient is given points as shown in the table. A diagnosis of definite NF1 is established if the total number of points is 6 or more (Baser et al. 2011).
represent one of the most serious complications of NF1. They may be continuous with intracranial or intraspinal tumours. Plexiform tumours of the periorbital area, which occur in 5% of patients, can produce proptosis and visual compromise. Large plexiform neurofibromas occur in 25–32% of patients (Huson et al. 1988; North 1998; Darrigo 2007) and tend to grow larger with age. The cosmetic burden may be considerable, and large cervical lesions may displace and compress vascular and respiratory structures and be life threatening. Treatment is surgical but difficult so other methods are being studied (Packer and Rosser 2002; Robertson et al. 2012). One case of sudden death secondary to a neurofibroma of the Xth nerve is on record (Chow et al. 1993). Plexiform neurofibromas of the limbs may be associated with partial gigantism. Involvement of the face is possible and may be associated with exophthalmos and rarely with unilateral megalencephaly (Cutting et al. 2002). Such lesions may be associated with bony abnormalities of the orbit; they require rapid treatment if the eyelid completely covers the eye, to avoid secondary amblyopia. Most plexiform neurofibromas appear before 2 years of age and some may be present at birth. Involvement of the iris by pigmented hamartomas known as Lisch nodules is specific for NF1. Lisch nodules are found in 22–30% of patients with NF1 by 6 years of age and in virtually all after age 12 years (Flueler et al. 1986; North 1998).

**Neurological Manifestations of NF1**

Neurological manifestations of NF1 are protean and include intellectual disability, specific learning difficulties and symptoms and signs due to intracranial and intraspinal tumours (North 1998, 2000; Evans et al. 1999; Friedman 2002). Macrocephaly (>98th centile) is present in only 16–45% of children with NF1 (Huson et al. 1988; North 1997) and is not correlated with neurological or neuropsychological difficulties (Cutting et al. 2002). It is due to megalencephaly and is not accompanied by symptoms of increased intracranial pressure. Headache occurs in over half the patients and may be migraine-like.

Specific learning difficulties are a well-known feature of NF1 (Riccardi 1992). Intellectual disability is relatively uncommon: Riccardi put the frequency at 8% but lower figures have been reported by other authors (North 1997; North et al. 2002). However, the IQ of patients with NF1 is on average lower than that of non-affected siblings. Specific learning difficulties are a common problem, being present in 32% (Hofman et al. 1994) to 65% (North et al. 1998) if impaired academic performance is taken as the criterion. Depressed performance in verbal tasks and a high incidence of language deficits are particularly obvious, but all areas of cognition can be affected (Cutting et al. 2000). Attention-deficit disorder without hyperactivity is common and may respond to amphetamine therapy. A study by Templer et al. (2013) suggested that children with NF1 experience problems with executive functioning that are not wholly accounted for by the behavioural features of attention-deficit–hyperactivity.
disorder. A significant association of cognitive deficits with the presence of T2-intense areas on magnetic resonance imaging (MRI) has been reported by several investigators (Denckla et al. 1996; Wang et al. 2000; Goh et al. 2004) but not by others (Moore et al. 1996; Rosenbaum et al. 1999). Although further studies may still be needed there is increasing evidence correlating the presence of unidentified bright objects with cognitive dysfunction (Feldmann et al. 2010; Piccitelli et al. 2012). Social skills have been shown to be frequently affected with resulting difficulties in communication (Barton and North 2004). Behavioural difficulties are also common (Kayl and Moore 2000). A recent population based study reported a prevalence of autism spectrum disorder (ASD) of 30% (Garg et al. 2013).

Epileptic seizures are more frequent in children with NF1 than in the general population, but available figures vary between 3.5% (North 1998), 4.2% (Kulkantrakorn and Geller 1998) and 7.3% (Huson et al. 1988). All types of seizures including infantile spasms (Motte et al. 1993; Fois et al. 1994; Ruggieri et al. 2009; Ostendorf et al. 2013) may occur. Focal seizures are more often observed than generalised seizures (Hsieh et al. 2011). Electroencephalogram (EEG) abnormalities are seen in 15% of patients (Riccardi 1992).

Epilepsy in NF1 has been reported to be relatively easy to control with antiepileptic drugs (Hsieh et al. 2011) with approximately 60% of patients having good seizure control (Vivarelli et al. 2003). However, in a recent study, only 16 of 47 (33%) patients with NF1 with epilepsy received only one antiepileptic drug, while 77% of individuals with structural abnormalities on MRI needed more than one drugs (Ostendorf et al. 2013).

In NF1 the occurrence of epileptic seizures could be related to intracranial glioneuronal tumours (gliomas and dysembryoplastic neuroepithelial tumours) and malformations of cortical development, but not to neurofibromatosis unidentified bright objects (Hsieh et al. 2011; Barba et al. 2013). Malformations of cortical development are encountered with lower frequency in comparison to other neurocutaneous syndromes and present in the form of polymicrogyria, focal cortical dysplasia, and hippocampal sclerosis (Mastrangelo 2009; Barba et al. 2013). Hemimegalencephaly has been reported (Cusmai et al. 1990). Epilepsy surgery can be performed effectively in patients with NF1 provided a single and well delimited epileptogenic zone is recognised. The high prevalence of dysembryoplastic neuroepithelial tumours (DNETs) in the series reported by Barba et al. (2013) might suggest a nonfortuitous association with NF1.

Optic gliomas (see Chapter 14) are present in 15–20% of patients with NF1 (North 1998). Historically, they may differ from other optic gliomas by the presence of an arachnoidal gliomatosis surrounding the optic nerve (Seiff et al. 1987) but otherwise they are typical pilocytic astrocytomas. They may be limited to the optic nerve or involve the chiasm and the retrochiasmatic portion of the visual pathway. Between 10% and 60% of optic gliomas are associated with NF1. The proportion tends to increase in the case of bilateral gliomas, which are almost exclusively found in patients with NF1. Clinical manifestations include ptosis and diminished visual acuity, but many gliomas are now discovered by systematic neuroradiological evaluation. Up to 39% of patients present with precocious puberty (Habiby et al. 1995). The proportion of symptomatic patients is 20–30%, and most symptomatic patients manifest before age 6 and often by 2 years of age (Listernick et al. 1994, 2007).

Optic gliomas in NF1 fall into two groups: those that remain stable, and those that are active, increase in size and threaten vision. Only 52% of patients whose optic gliomas were detected by MRI developed symptoms (Listernick et al. 1997). Emergence of symptoms after age 6 years is extremely rare, as is progression beyond age 10, although a few people who show late presentation or late progression are on record (Listernick et al. 2004). Even in symptomatic patients the outcome is often favourable, and this has to be taken into account for therapeutic indications and for those of repeated imaging. Guillaumo et al. (2003) found a favourable outcome in a majority of 104 patients with NF1 (88 of whom were children) with CNS tumours, including 88 optic gliomas, 55 of which were symptomatic. This high proportion of symptomatic patients is explained by the surgical origin of this study. Intraorbital gliomas only rarely spread intracranially. The evolution of optic gliomas in NF1 may be more benign than in isolated patients (Listernick et al. 1994) but there is no universal agreement in this regard. Tumours anterior to the chiasm frequently remain stable, whereas more posteriorly located gliomas are more often invasive (Hernández Driever et al. 2010). The diagnosis of optic glioma may be suggested by finding an enlarged optic foramen, although this sign is not specific as elongation of the optic nerve and dural ectasia can simulate a tumour (Riccardi 1992; North 1997).

Modern neuroimaging has transformed the conditions of diagnosis of optic pathway tumours in patients with NF1 (Fig. 4.2) There is an ongoing controversy about the indications for imaging in NF1 (Di Mario et al. 1993). Expert physicians agree that symptomatic cases should be scanned. For asymptomatic people with NF1, the National Institutes of Health Consensus Development Conference (1988) did not advise systematic study as no treatment is usually indicated. Riccardi (1992) is of the opposite opinion, as some aggressive gliomas may progress silently for relatively long periods and may cause damage that could be prevented by early diagnosis. Monitoring of visual evoked potentials may permit early detection but there is a high level of false positives. A study by Yerdelen et al. (2011) on 39 adults and adolescents revealed that over half had abnormal visual evoked potentials even with normal MRI. This could represent either an early presentation of optic glioma or be due to an abnormal myelinisation of the visual pathway.

Treatment of optic glioma is still controversial (Riccardi 1992) (see also Chapter 14). Most tumours that appear stable, especially if localised to the anterior optic pathways, should be watched carefully without surgical or other intervention. In a collaborative study, extension to the optic chiasm was seen in only four of 106 unilateral cases (Wilson 1998). For optic
nerve gliomas that are growing and produce marked proptosis with complete unilateral loss of vision, surgical removal gives satisfactory results. For lesions that are not stable, radiotherapy is effective. However, irradiation with doses of 52 Gray, as usually required, is associated in children with intellectual disability and with endocrinological sequelae in one-third of patients. For patients under 5 years of age whose sensitivity to radiation is particularly high, chemotherapy tends to be substituted for radiotherapy. Combinations of vincristine and carbiplatin have been found effective and are often used (North 1997).

Other intracranial tumours are less common (Fig. 4.3). They are mostly astrocytomas that can involve the hemispheres, cerebellum, basal ganglia or brainstem. Brainstem tumours accounted for 21% of intracranial tumours in patients with in the large series of Guillamo et al. (2003). These are of special interest because their prognosis is usually much better than that of brainstem tumours unassociated with NF1. Molloy et al. (1995) studied 17 patients. In only six of these was there evidence of progression by imaging, and in only three was progression detectable clinically. The tumours involved the medulla in 14 patients. Fifteen of the patients were alive at

![Figure 4.2](image1.png)

**Figure 4.2** Neurofibromatosis type 1 in a 3-year-old girl with bilateral optic pathway tumor (optic glioma). (a) T2-weighted sagittal and (b) axial images with asterisks showing infiltration of optic chiasma.

![Figure 4.3](image2.png)

**Figure 4.3** (a) T2-weighted and (b) FLAIR axial MRI scans in a 15-year-old girl showing large mixed solid and cystic tumoral lesion involving the right temporal lobe associated with surrounding oedema, which was found to be a high-grade glioma at surgical biopsy (asterisks). Note also hyperintensity of the left hippocampal cortex and anterior part of the left pallidum in a context of neurofibromatosis type 1 (arrows).
follow-up after several years, although no treatment other than a shunt when required was given. The authors concluded that these lesions are intermediate between hamartomas and classic brainstem tumours, and that aggressive treatment is best withheld unless there is evidence of progression on monitoring. Pollack et al. (1996) came to similar conclusions in a study of 21 patients. Schmandt et al. (2000) reported spontaneous regression of some astrocytomas. A study on gliomas in 100 patients with NF1 (24 of them arose in the optic pathways) concluded that those tend to be lower grade and have a more favourable prognosis than in patients without NF1, with pilocytic astrocytomas and low-grade astrocytomas (subtype intermediate) being most common. However, diffusely infiltrating astrocytomas are also seen in a subset of patients and need to be managed accordingly (Rodriguez et al. 2008). Multiple brain tumours are not uncommon (Flohstrasser et al. 1988). Intracranial calcification involving the central nuclei or the periventricular area is rare (Arts and Van Dongen 1986) and is not of tumoural origin.

Malignant peripheral nerve sheath tumours are also not uncommon in adolescents and adults (lifetime risk 10%) and patients carry a poorer prognosis than patients without NF1 (Porter et al. 2009). They are rare in children but do occur (Drouet et al. 2004). They have been identified as a leading cause of death in adulthood in patients with NF1.

Intraspinal tumours, comprising mainly astrocytomas, are uncommon. Intraspinal neurofibromas occur mainly in the cervicothoracic region. These tumours not uncommonly are both intra- and extraspinal and may be in continuity with a subcutaneous plexiform neurofibroma. Intramedullary tumours such as ependymomas and astrocytomas are not a feature of NF1. Rare cases of spinal neurofibromatosis with multiple symmetrical tumours are on record (Pascual-Castroviejo et al. 2007).

The so-called ‘unidentified bright objects’ are hyperintense areas especially demonstrated by MRI, most frequently on T2 sequences in the thalami, the pallidum, the cerebellar peduncles and hemispheres, but also in the hemispherical white matter in the optic tracts and radiations (Fig. 4.4). The significance of this finding is not fully understood. Such areas, in most patients, do not correspond to tumour extension, although in the past they have been described as ‘hamartomas’ (Braffman et al. 1988) and may remain stable or disappear. They are frequent in patients without, as well as those with, optic pathway gliomas (Duffner et al. 1989; North 1998). North (1997) found high-intensity T2 lesions in 32 of 50 systematically studied 8–16-year-old patients, 24 of whom had no tumour. The lesions were usually multiple, involved the optic tract in 20 patients, the basal ganglia in 24, the cerebellum in eight and the brainstem in six. Hyperintense lesions were seen in T1-weighted sequences in 16 children, usually corresponding with T2 abnormalities. As a result of improvement in magnetic resonance techniques the frequency of these abnormalities has been even higher in recent series, and some authors have proposed them as a diagnostic criterion for NF1 (Curless et al. 1998; DeBella et al. 2000). They were present in 25 of the 29 patients described by Rosenbaum et al. (1999) and in 89% of those of Raininko et al. (2001). The latter authors made a detailed study of these areas. They found them more commonly on proton density (80%) than on T1 (50%) sequences and noted that they occasionally enhanced with gadolinium. In five of their patients they increased in size, with later regression and disappearance in four. They often change with evolution, tending to disappear with age, although they may increase in number at adolescence, as also found by Kraut et al. (2004) who reported a biphasic evolution. They are not more common when an optic pathway tumour is present. Hyperintense areas tend to decrease and often disappear before adulthood (Sevick et al. 1992). Their histological nature is unknown. They are more common in children and adolescents than in adults. Those located in
the optic tracts and the pallidum are larger than those found elsewhere and may give an abnormal signal, although a weak one, on T1-weighted images (Inoue et al. 1997). The abnormally intense T2 areas have been shown in a few patients to represent glial dysplasia or spongiotic changes rather than hamartomas (Di Paolo et al. 1995). Proton MRI of such lesions (Wang et al. 2000) showed initially an increase in choline and relatively normal N-acetylaspartate, later followed by a decrease in N-acetylaspartate, suggesting a secondary loss of neurons. Billiet et al. (2014) studied the microstructure of tissue with in vivo MRI-based techniques. Their results support the hypothesis of intramyelinic vacuolisation, in the absence of demyelination or axonal damage.

Hydrocephalus in a majority of patients is the result of aqueductal stenosis (Afifi et al. 1988; Riviello et al. 1988). It usually develops slowly and is recognised late. It is most commonly due to gliosis, diffuse or membranous, of the aqueduct. Small tumours of the peduncular region may be a cause, and MRI in the sagittal plane using both T1- and T2-weighted sequences should always be performed. An intense signal in T2-weighted scans was present in seven of nine patients (Pou Serradell and Ugarte-Elola 1989; Valentini et al. 1995). Other causes of ventriculomegaly in patients with NFI include Chiari I malformation (Afifi et al. 1988) and tumours of the posterior fossa.

Other Complications of NF1

These include growth retardation, which was reported in about 25% of patients by North (1998). Vassilopoulou-Sellin et al. (2000) found that 122 of 251 children were below the 25th centile and 68 were below the 10th centile for age. Eye disease, especially glaucoma and buphthalmos, osseous dysplasia and arachnoid cysts are classic findings. Abnormalities of the skull are frequent in NF1. Craniofacial dysplasia can affect any portion of the cranial vault, most commonly the occipital regions along the lambdoid suture. Bones contributing to the orbit, especially the greater sphenoidal wing, are a site of election for dysplasia. The greater wing is missing in part, with resulting pulsating exophthalmos when the defect is large. The lesser wing and sella turcica are often involved in the dysplasia. Dural ectasias can produce bilateral enlargement of the auditory canal, which may suggest the diagnosis of NF2, but they are not associated with schwannoma of the VIIIth nerve (Inoue et al. 1997). Calvarial defects adjacent to the lambdoid suture are clinically asymptomatic.

Scoliosis is present in 20% of patients and may be sufficiently severe to warrant surgical correction. It is occasionally associated with paraspinal neurofibromas. Vertebral abnormalities are frequent, and scalloping of the body of vertebrae is a common radiological finding in NF1, as is scoliosis. Lateral ectasia of the thinned dura through the intervertebral foramina (lateral meningoceles) is a rare complication of NF1 (Riccardi 1992). Tibial pseudarthrosis is a common lesion (North 1997). Decreases in bone mineral density, even osteoporosis can be identified in individuals with NF1, perhaps even as early as childhood (Brunetti-Pierri et al. 2008; Stevenson et al. 2008).

Vascular manifestations (Tomsik et al. 1976) include systemic hypertension with or without renal artery stenosis, which should always be looked for, and, rarely, cerebrovascular accidents (Rosser et al. 2005). Multiple stenoses of carotid arteries with the development of a moyamoya pattern has been reported (Rizzo and Lessell 1994). Grill et al. (1999) observed that 13 of 69 children who received X-irradiation for glioma of the optic chiasma developed vascular stenosis of the intracranial carotid arteries.

The incidence of malignancies, the most frequent of which are fibrosarcomas, is higher in persons with NF1 than in the rest of the population, but they are rare in childhood. Leukaemia, especially of chronic myelogenous type, can occur (Clark and Hutter 1982) and may be associated with the presence of cutaneous xanthomas. Visceral and endocrine tumours are relatively common in later life (Huson et al. 1988). Visceral autonomic localisations may be seen. In particular, intestinal ganglioneuromatosis with intestinal obstruction is recognised (Kim and Kim 1998).

Course of NF1

The course of NF1 is very variable and minor forms are common. However, many complications can occur and mortality is not negligible, especially when subcutaneous neurofibromas are present. Khosrotehrani et al. (2005) found 40 deaths in a 2.6 year follow-up of a series of 703 patients, 57.6% of whom were children. In this series, the presence of cutaneous neurofibromas was associated with a significantly higher mortality. In a 10-year follow-up study of 150 patients, Cnossen et al. (1998) showed that 41% of them developed complications during this period; 28% had one complication, 12% had two and 1.3% had three. All patients should, therefore, be followed regularly, even in the absence of symptoms. Life expectancy in NF1 is approximately 8 years lower than the general population (Wilding 2012).

Diagnosis of NF1

The diagnosis of NF1 is essentially clinical and by imaging (Table 4.1) and it is usually easy. Histological study of pigmented spots could show abnormalities in melanomas (Martuza et al. 1985), but it is not usually justified. Imaging diagnosis may be difficult, and MRI is the primary tool for the diagnosis of CNS abnormalities. NF1 genetic testing is reserved for unusual presentations or reproductive decision-making.

Management of NF1

The management of patients with NF1 should start with assessment of the extent of the disease by a complete clinical, ophthalmological and radiological examination. A team
approach, grouping specialists in the many different problems that are often associated with the condition, is important, as it has been shown that many patients are not appropriately diagnosed and treated for all their problems. A thorough search for neurological, visceral and bone abnormalities is essential. Careful clinical follow-up is mandatory. Huson (1999) thinks a consultation every 2 years is reasonable, but closer surveillance and complementary investigations are required when symptoms appear. Members of the United Kingdom Neurofibromatosis Association Clinical Advisory Board recommend that the following should be recorded at each annual visit: development and progress at school; visual acuity and fundoscopy until age 7 years (optic pathway glioma, glaucoma); head circumference (for a rapid increase indicating tumour or hydrocephalus); height; weight; pubertal development (delayed/precocious puberty due to pituitary/hypothalamic lesion); blood pressure (renal artery stenosis, pheochromocytoma); cardiovascular examination (congenital heart disease, especially pulmonary stenosis); evaluation of spine (scoliosis underlying plexiform neurofibromas); evaluation of the skin and system examination guided by specific symptoms (Ferner et al. 2007).

Whether routine imaging studies of the CNS are required remains disputed, they generally seem to be performed at least on the first examination. Repeated studies should be undertaken according to clinical indications. It is clearly necessary for those patients who have suspected brain tumours. For patients with known optic gliomas, at least an annual surveillance and complementary investigations are required when symptoms appear. Members of the United Kingdom Neurofibromatosis Association Clinical Advisory Board recommend that the following should be recorded at each annual visit: development and progress at school; visual acuity and fundoscopy until age 7 years (optic pathway glioma, glaucoma); head circumference (for a rapid increase indicating tumour or hydrocephalus); height; weight; pubertal development (delayed/precocious puberty due to pituitary/hypothalamic lesion); blood pressure (renal artery stenosis, pheochromocytoma); cardiovascular examination (congenital heart disease, especially pulmonary stenosis); evaluation of spine (scoliosis underlying plexiform neurofibromas); evaluation of the skin and system examination guided by specific symptoms (Ferner et al. 2007).

Surgical treatment is indicated only for invasive tumours as much of the tumours are either static or slowly growing, but the results are often disappointing. The same applies to radiotherapy, as sequelae are particularly prone to occur in young children. Epileptogenic tumours can be treated surgically, provided that a link is clearly established with the electroclinical presentation of the seizures. Surgery is also indicated for visceral lesions, cosmetic deformities and orthopaedic problems that in many cases amount to a major problem. There is no drug treatment for neurofibromatosis, although several drug trials have been initiated, in an attempt to slow or halt the growth of neurofibromas. Some studies were done to assess the efficacy of statin use in improving cognitive function in children with NF1 but results are contradictory (Krab et al. 2008; Acosta et al. 2011; van der Vaart et al. 2013).

Several clinical trials have been initiated, including studies of imatinib (Robertson et al. 2012) or sorafenib for plexiform neurofibromas, bevacizumab and everolimus for malignant peripheral nerve sheath tumours, everolimus for progressive glioma associated with NF1, and mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitors for children with inoperable plexiform neurofibromas (Hirbe and Gutmann 2014; Plotkin et al. 2014).

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### NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis Type 2 (NF2) is transmitted as a dominant autosomal trait. The gene has been mapped to chromosome 22 (Rouleau et al. 1993). Bilateral acoustic neuromas (vestibular schwannomas) are the essential feature, occurring in at least 90% of patients (Evans et al. 1992a). These tumours develop mainly in late adolescence and early adulthood, and NF2 is rarely found in children. Loss of hearing is the first symptom. Cutaneous manifestations are uncommon and most patients have no café-au-lait spots, or only a small number of them. Some of these are schwannomas. Histologically they differ from those in NF1; they are usually less than 2cm in diameter, slightly raised, well circumscribed, and may contain excess hair (MacCollin and Mautner 1998; Ruggieri et al. 2005). Lisch nodules are not found, but posterior subcapsular cataracts occur in 10% or more of patients (Ruggieri et al. 2004). Other intracranial tumours are frequent especially meningiomas, often multiple but optic nerve glioma has not been found in NF2 patients. The occurrence of astrocytoma also seems to be exceptional. Diagnostic criteria are summarised in Table 4.1. Definite diagnosis is based on MRI findings (Fig. 4.5).

Schwannomas of cranial nerves V to XII are common. They are frequently bilateral and multiple. Some authors indicate that atypical NF2 may occur sporadically and often presents with multiple cranial or spinal schwannomas (Purcell and Dixon 1989; Pou Serradell 1991). MacCollin et al. (1996) proposed separating a subgroup of NF2 under the term ‘schwannomatosis’, manifested by peripheral painful nerve schwannomas and often by multiple spinal root tumours. Such cases may be difficult to distinguish from children with NF2 in which peripheral tumours may long precede the appearance of acoustic schwannomas, and indeed have been shown to be a variant of NF2 (Evans et al. 1997).

Spinal cord tumours are of two types: schwannomas, which are of the same histological type as the acoustic neuroma, and ependymomas (Rubinstein 1986). The former may be multiple and lead to serious problems. Hamartomatous lesions resembling meningiomas, termed ‘meningoangiomatosis’ (Russell and Rubinstein 1977), may occur and be responsible for calcification, especially in the choroid plexus, at the periphery of one cerebellar hemisphere (Ruggieri et al. 2005), or as linear subependymal calcification (Arts and Van Dongen 1986), which may be associated with seizures. Involvement of peripheral nerves can occur. Presymptomatic diagnosis is possible with chromosome 22 markers (Ruttledge et al. 1993).

Ruggieri et al. (2013) described the natural history of three unrelated children with bilateral vestibular schwannomas due to NF2 and detected incidentally on brain MRI at ages 4–5 months. These children had no symptoms for a period of 11–15 years, when their schwannomas became symptomatic. During the period in which their schwannomas remained asymptomatic, these children developed NF2 plaques, mostly
in atypical locations, which spontaneously resolved by the age of 11–15 years. Retinal changes and lens abnormalities were detected in two of these children as early as 3 months of age (Ruggieri et al. 2013).

NF2 is a separate disorder from NF1 and there are a few patients with both NF1 and NF2 inherited separately from each parent (Evans et al. 1992b). The disease may be mistaken for NF1 in the rare patient with bilateral auditory canal enlargement without tumour (Kitamura et al. 1989). The presence of bilateral acoustic neuromas in NF1 has, however, been reported (Pou Serradell 1991).

The management of NF2 should be supervised by a specialist team. It includes regular assessment, looking especially for acoustic nerve tumours. Special attention should be given to monitoring of hearing as acoustic neuromas usually occur relatively late. Surveillance for other tumours and ocular problems should also be regularly performed. Early assessment of siblings may allow effective treatment of ocular abnormalities and should be systematically offered. A first MRI of patients is indicated from 10 to 12 years of age (Evans et al. 2003).

OTHER FORMS OF NEUROFIBROMATOSIS

SEGMENTAL NEUROFIBROMATOSIS

Segmental Neurofibromatosis (NF5) is closely related to NF1. NF5 is characterised by the unilateral occurrence of features that are typical of NF1 (café-au-lait spots and neurofibromas) in only one or in several dermal segments. The disorder is thought to result from a postzygotic mutation event, and any dermatome may be involved (McLimore et al. 2014). Most cases are sporadic although familial transmission has been observed (Jung 1988). Although NF5 is said to be rare, Listernick et al. (2003) reported 39 patients from three centres. In 29 of these the disease was limited to pigmented disorder with café-au-lait spots, isolated in eight patients or associated with axillary freckling. Other abnormalities are rare but iris nodules or pseudarthrosis may be found in the affected segments (Ruggieri et al. 2005).

Roth et al. (1987) divide segmental neurofibromatosis into four subtypes, only one of which is genetically transmitted. The skin lesions are usually café-au-lait patches but neurofibromas may eventually develop. Other complications of neurofibromatosis do not occur. The prognosis is good.

OTHER POSSIBLE FORMS

Forms with only café-au-lait spots and other atypical forms are on record. Charrow et al. (1993) found suggestive evidence of non-linkage to the NF1 locus, but Abeliovich et al. (1995) found close linkage to the NF1 gene in a large pedigree. Intestinal neurofibromatosis may occur in isolation (Heimann et al. 1988) or form a part of syndromes related to neurofibromatosis and to the multiple endocrine neoplasia disorders (Fryns and Chrzanowska 1988; Griffiths et al. 1990). Type III or IIB multiple endocrine adenomatosis is characterised by a Marfan-like habitus, a lobulated tongue with multiple submucous neuromas, conjunctival nodules, thick lips, megacolon and multiple endocrine tumours (Moline and Eng 2011).

Legius syndrome concerns patients with a mild NF1 phenotype with pigmentary changes. However, these patients do not develop neurofibromas or Lisch nodules and present...
mutations in SPRED1 gene (Brems et al. 2007; Messiaen et al. 2009).

A combination of NF1 with features of the Noonan phenotype (short stature, pectus carinatum, cardiac defect, proptosis and low intelligence) has long been known and has been termed ‘neurofibromatosis–Noonan syndrome’ (Borochowitz et al. 1989). Baralle et al. (2003) found that two of six patients had novel mutations in the NF1 gene and no mutation in the PTPN11 gene, thus indicating that some of these people have NF1. The frequency of NF1 mutation in such patients was recently confirmed (De Luca et al. 2005; Ekvall et al. 2014). However, Bertola et al. (2005) and Thié et al. (2009) found in some patients the coexistence of NF1 mutation and a PTPN11 mutation known to cause Noonan syndrome. Watson syndrome (café-au-lait patches and pulmonic stenosis), which may include CNS involvement in the form of areas of increased T2 signal (Leão and da Silva 1995), is probably allelic to NF1 (Tassabehji et al. 1993).

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is an autosomal dominantly transmitted disorder characterised by hamartomas that can affect many organs including the skin, brain, heart, kidneys and other sites, with a variable expression. TSC has a high incidence of new mutations in the order of 58–68% of recognised patients (Hunt and Lidenbaum 1984). The prevalence of the disease is imperfectly known because of the frequency of paucisymptomatic forms. Population surveys indicate a prevalence of 1 in 6000 to 1 in 10 000 (Kuntz 1988; Webb and Osborne 1995). Occurrence of affected siblings with apparently unaffected parents is rare. Two genes are responsible for TSC. In about 25% of the families TSC is caused by a mutation in the TSC1 gene in chromosome 9q34.3 that codes for the protein hamartin; in the remainder the TSC2 gene in 16p13.3 that encodes the protein tuberin is affected. Both genes probably act as tumour suppressor genes (Au et al. 2004) and are involved in neuronal specification and migration. In 490 people with TSC Sancak et al. (2005) found the TSC2 gene responsible for TSC in 78%, 3.4 times more often than TSC1. TSC1 mutations account for 10–30% of affected families, whereas most cases of TSC2 mutations are observed in sporadic cases. TSC2 mutations, tend to be more severe (Kothare et al. 2014). No mutation is detected in 15–20% of patients, who usually show a milder clinical disease.

The mechanism of the disease involves an abnormality of proliferation and differentiation of embryonic cells, with a tendency to hamartomatous proliferation, and a disturbance of the migrational process of CNS cells resulting from the disruption of either hamartin or tuberin. These proteins act as sensors for growth factors, linking the extracellular cues to the activity of mTOR, a major regulator of protein translation and cell growth. Growth factor receptors activate a cascade regulating a large number of cellular functions (Goh and Weis 2006). Work in the past few years has considerably increased our understanding of the disorder, especially the role of reduced inhibition of the mammalian target of rapamycin (mTOR) activation factor (Crino et al. 2006). Tuberin and hamartin function together forming a TSC2: TSC1 tumour suppressor complex. This complex is the principal cellular inhibitor of the mammalian target of rapamycin, mTOR (Orlova and Crino 2010).

Pathology and Pathogenesis of TSC

The characteristic lesions found in the brain of patients with TSC are cortical tubers, subependymal nodules and giant cell tumours. Tubers (Fig. 4.6) are hard nodules of variable size that show disruption of normal lamination, increased astrocytic nuclei and a reduction of the number of neurons, which are replaced by bizarre giant cells (Huttenlocher and Heydemann 1984; Yamanouchi et al. 1997) that take both glial and neuronal markers. They may become calcified. Beneath the tubers, enlarged abnormal heterotopic neurons extend all the way to the ventricular walls. Subependymal nodules are small excrescences on the ventricular walls that resemble solidified wax that has dripped down the side of a candle; hence the term ‘candle guttering’ that is traditionally used. They are composed of large round fusiform cells that are thought to be of astrocytic origin. Subependymal giant cell astrocytomas (Fig. 4.7a–f) are found in about 5% of patients (Gomez et al. 1988) and are consistently located to the region of the foramen of Monro. Unlike subependymal nodules, they tend to measure over 5mm and to be less homogeneously dense; they sometimes grow to a large size but rarely if ever, become malignant. The nature of the giant cells is still uncertain (Sharma et al. 2004).

Visceral tumours arise from various visera. Rhabdomyomas are found in the heart of 40–50% of patients with TSC and are often multiple. Renal lesions include angiomylipomas, which may be the only lesion of TSC in some patients, and renal cysts (Robbins and Bernstein 1988). Retinal phakomas are benign astrocytic tumours that tend to calcify. Other hamartomatous lesions are seen less commonly (Gomez et al. 1988).

Clinical Manifestations of TSC

The clinical manifestations of TSC vary considerably with the extent of involvement and age at onset. Table 4.2 groups the findings into those that are highly suggestive and those that are less characteristic of the disease, according to the revised criteria (Gomez et al. 1988; Roach et al. 1998). Because no feature is pathognomonic, involvement of two organ systems or at least two dissimilar lesions in the same organ is required for diagnosis (Roach and Sparagana 2004). The
most recent revision in June 2012 includes genetic criteria and eliminates probable disease as a diagnostic class. The diagnosis now is definite if a pathogenic mutation of TSC1 or TSC2 is identified or if two major features or one major feature with two or more minor features are present. The diagnosis is possible if either one major feature or two or more minor features are present (Northrup and Krueger 2013).

**Epilepsy in TSC**

In infants and children, seizures are the most common presenting symptom, occurring in around 80% of patients. The majority (70%) of patients start under the age of 12 months with lesser occurrence with age: 16%, 1–4 years; 9%, 5–15 years; only 4% begin their epilepsy over the age of 16 years (Cross et al. 2005). Infantile spasms (Gomez et al. 1988; Curatolo and Seri 2003) are the most common type of seizures in infancy. Vigabatrin can be particularly useful in this case, with a response rate of 95% compared to 54% of children with a non-TSC aetiology of spasms (Cross et al. 2005). Other types of seizure are not unusual, especially focal motor seizures. Tonic or atonic seizures are also frequently seen in children who progressively develop Lennox–Gastaut syndrome. Multiple types of seizures are present in 50% of patients, and drug resistance may occur in about 37–62% (Chu-Shore et al. 2010; Vignoli et al. 2013). About 5% of patients, especially those with a TSC2 mutation, can have epileptic spasms, occurring outside the age range of the first 2 years (Hsieh et al. 2013).

Selected individuals should be considered for epilepsy surgery, especially if seizures arise from a single tuber. The decision on type of presurgical evaluation has to be taken by teams with experience in paediatric epilepsy surgery. A stereo-EEG investigation is usually necessary in children with multiple tubers. A meta-analysis of 20 studies looking at results of epilepsy surgery in TSC, reported the following as statistically significant predictors of good postoperative outcome: absence of generalised seizure semiology, no or mild developmental delay, unifocal ictal scalp EEG abnormality and EEG/MRI concordance (Fallah et al. 2013). Another meta-analysis of 13 studies also found that patients with unilateral focal ictal-interictal EEG abnormalities, with seizure onset later than 1 year of age and extensive resection (lobectomy), had a higher rate of seizure freedom (Zhang et al. 2013). Completeness of resection, focal scalp interictal EEG patterns, agreement of interictal and ictal EEG localisation, one-stage surgery and few tubers were good predictive factors of seizure-free outcome after surgery according to another study in 33 TSC patients (Krsek et al. 2013). The identification of the most active and epileptogenic tubers may be obtained by a multimodal presurgical evaluation, including invasive EEG monitoring. Unfortunately, seizures may persist after tuberectomy and they may arise in the future from other tubers.

A study with intracranial electrocorticography revealed that the epileptiform activity started from the surrounding perituber cortex while tubers were electrically silent (Major et al. 2009). But the study by Mohamed et al. (2012) exploring intracranial EEG findings, suggested that tubers play a
greater role in seizure genesis than perituberal cortex, and that tuberectomy may be a sufficient surgical approach in a number of patients.

Everolimus (the inhibitor of the mammalian target of rapamycin complex 1mTORC1), with demonstrated benefit for TSC-related renal angiomyolipoma, lymphangiomatosis and subependymal giant cell astrocytoma (SEGA), has been tried in a prospective, multicentre, open label study showing a median reduction of seizure frequency of 73% in 17 of 20 treated participants (Krueger et al. 2013). A much larger prospective study is currently ongoing.

**Neurodevelopmental difficulties in TSC**

Intellectual disability is the rule in hospital-based series and was present in 82% of children in one study (Monaghan et al. 1981). However, in the Mayo Clinic experience, only 47% of patients and their affected relatives were judged to have below normal intelligence, while 44% had normal intelligence (Gomez et al. 1988). Webb et al. (1991) gave an even lower figure for intellectual disability (40%) in a population study. Intellectual disability is found mainly in patients who have had seizures, and especially where these had their onset before 2 years of age (with an even worse prognosis for a history of infantile spasms) (Gomez et al. 1988; Chu-Shore et al. 2010; Humphrey et al. 2014). The prognosis of infantile spasms in patients with TSC is thus serious compared to other forms of epilepsy, even though a proportion of these patients may develop a normal cognition (Rando et al. 2005; Jóźwiak et al. 2011). Riikonen and Simell (1990) found that infantile spasms due to TSC have an especially poor prognosis, while Yamamoto et al. (1987) reported that the outcome in such patients was significantly better than that of patients with symptomatic spasms due to other causes. Bolton et al. (2015) support the proposition that severe, early-onset...
epilepsy may impair intellectual development in TSC and highlight the potential importance of early, prompt and effective treatment.

In addition to intellectual regression and/or disability other behavioural or cognitive abnormalities such as specific cognitive deficits and hyperkinesia are not infrequently found in patients with TSC (Hunt and Dennis 1987).

Autism is a frequent feature of TSC, especially in those children who had infantile spasms (Bolton 2004). It is present in 25–50% of patients and TSC may be responsible for 1–4% of cases seen in the population (Wiznitzer 2004). Burket et al. (2015) stipulate that the severity of intellectual disability and ASD in TSC may relate more to the underlying metabolic disturbance (over activity of mTOR signalling), as shown by improvement of sociability and other symptoms in mouse models treated with rapamycin. Gipson et al. (2015) described in detail, the neurodevelopmental phenotype of three individuals with TSC and concluded that they shared common characteristics. They identified a distinct profile of ASD order specific to TSC that requires consideration before diagnosis of autism and can help optimise treatment across the life span. But other authors reported that children with TSC and ASD demonstrated a profile of social communication impairment that has complete convergence with children presenting non-syndromic ASD (Jeste et al. 2016). The authors suggest the need for early intervention in toddlers with TSC, with treatment strategies targeting social communication function as well as broader developmental domains, before the onset of autism symptoms. Concerning treatment, everolimus, an mTOR inhibitor, was observed to lower rates of self-injury in one patient (Gipson et al. 2013).

Other neurological deficits in TSC are rare, with the exception of increased intracranial pressure that occurs in less than 5% of patients and results from the development of intraventricular giant cell tumours and becomes symptomatic after the

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<th>Table 4.2 Diagnostic criteria for tuberous sclerosis complex (TSC)*</th>
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<tr>
<td>Genetic diagnostic criteria</td>
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<td>1. The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g. out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g. large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (<a href="http://www.lovd.nl/TSC1">www.lovd.nl/TSC1</a>, <a href="http://www.lovd/TSC2">www.lovd/TSC2</a> and Hoogeveen-Westerveld et al. 2012 and 2013).</td>
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<td>2. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC.</td>
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<td>Note: 10–25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.</td>
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<td>Clinical diagnostic criteria</td>
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<td>Major features</td>
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<tr>
<td>1. Hypomelanotic macules (≥3; at least 5mm diameter)</td>
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<td>2. Angiofibromas (≥3) or fibrous cephalic plaque</td>
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<td>3. Ungual fibromas (≥2)</td>
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<td>4. Shagreen patch</td>
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<td>5. Multiple retinal hamartomas</td>
</tr>
<tr>
<td>6. Cortical dysplasias (sm)</td>
</tr>
<tr>
<td>7. Subependymal nodules</td>
</tr>
<tr>
<td>8. Subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td>9. Cardiac rhabdomyoma</td>
</tr>
<tr>
<td>10. Lymphangioleiomyomatosis (LAM) (c)</td>
</tr>
<tr>
<td>11. Angiomyolipomas (≥2)</td>
</tr>
<tr>
<td>Minor features</td>
</tr>
<tr>
<td>1. ‘Confetti’ skin lesions</td>
</tr>
<tr>
<td>2. Dental enamel pits (&gt;3)</td>
</tr>
<tr>
<td>3. Intraoral fibromas (≥2)</td>
</tr>
<tr>
<td>4. Retinal achromic patch</td>
</tr>
<tr>
<td>5. Multiple renal cysts</td>
</tr>
<tr>
<td>6. Nonrenal hamartomas</td>
</tr>
<tr>
<td>Definite diagnosis: Two major features or one major feature with ≥2 minor features</td>
</tr>
<tr>
<td>Possible diagnosis: Either one major feature or ≥2 minor features</td>
</tr>
</tbody>
</table>

*Updated by Northrup et al. (2013).
†Includes rubers and cerebral white matter radial migration lines.
‡A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
age of 5 years. These giant cell tumours may also be responsible for a hemiplegia.

**Cutaneous manifestations in TSC**

The classic cutaneous lesions (Fig. 4.8) of TSC are present in 80% of patients. Classic angiofibromas (adenoma sebaceum) that occupy symmetrical areas over the cheeks, nasolabial folds and chin are red papular lesions, found in 50% of patients; they are rare in infants and generally appear between 3 and 15 years of age. Hypomelanotic macules (achromic patches or ash-leaf spots) are the earliest and most frequent cutaneous sign of TSC and occur in 90% of patients (Fryer et al. 1990). They vary in number and size and are often present at birth, although they may become more visible and more numerous within a few months. They may be visible only under Wood’s light in fair-skinned patients, especially infants. Isolated, small hypomelanotic spots are nonspecific. They are present in 0.8% of typically developing newborn infants (Alper and Holmes 1983). The association of white spots with seizures, especially infantile spasms, is characteristic of TSC. A lock of depigmented hair may be an initial sign (McWilliam and Stephenson 1978). It results from the presence of a hypomel-anotic spot on the scalp. Other cutaneous signs are seen later in life. They include fibrous plaques, usually on the forehead or scalp, that can occasionally be the sole manifestation of the disease; shagreen patches (20–40% of patients) that consist of a slightly elevated plaque of epidermis with a granular surface and sometimes a yellowish-brown discoulouration and appear after a few years of life, commonly in the lumbar region; periangual fibromas that are a pathognomonic lesion but one that seldom occurs before puberty and then only in about 50% of patients; and molluscum pendulum in the cervical and lower facial region – not a specific lesion but quite unusual in childhood outside TSC. Café-au-lait spots are not more frequent in TSC than in the general population (Bell and McDonald 1985).

**Eye anomalies in TSC**

Eye findings are represented by retinal astrocytomas (phako-mas) (Fig. 4.9), which are found in half the patients and may be unique or multiple. They are round or oval in shape and become easy to diagnose when they calcify, assuming a typical mulberry appearance. They are seldom symptomatic and only a handful of symptomatic changes have been reported in the past few decades (Mennel et al. 2007). Other ophthalmological findings in patients with TSC include depigmented retinal areas, hypopigmented iris spots, hyaline or cystic nodules, cataracts and iris coloboma. An increased incidence of association with subependymal giant cell astrocytomas, angiofibrolipoma, cognitive impairment and epilepsy has been noted in the presence of retinal findings (Aronow et al. 2012).

**Other findings in TSC**

In some patients, the presenting manifestations are visceral rather than CNS ones (Franz 2004). A search for other localisations of TSC is always indicated. Kidney tumours (angiolipomas), usually multiple and bilateral, are present in 60–75% of patients and may precede nervous system manifestations in
infants, while hypertension may be the first feature in children (Robbins and Bernstein 1988). They are often highly vascular and can produce severe haemorrhage.

Patients with TSC may also manifest with autosomal polycystic kidney disease, as the polycystic kidney disease gene, PKD1, is located in close proximity to the TSC2 accounting for the occurrence of both conditions in case of large deletions (contiguous gene syndrome) (Brook-Carter et al. 1994).

Cardiac rhabdomyomas may be revealed by echography; they may occur prenatally or may only be revealed following administration of drugs such as carbamazepine. About half the cardiac rhabdomyomas are a manifestation of TSC. Conversely, more than 50% of patients with TSC have cardiac tumours. Many are asymptomatic but some may manifest as cardiac failure, although arrhythmia is more common. Contrary to most other manifestations they have a marked tendency to disappear with time. They may be the cause of embolic strokes, although this is disputed by Gomez (1989).

Other visceral manifestations, especially pulmonary involvement frequent in adults, are rare in children. They usually present in women in their third of fourth decade and can be complicated by pneumothorax, hemoptysis, chylothorax and respiratory failure. Partial gigantism has been reported in TSC (Franz 2004).

**Diagnosis of TSC**

The diagnosis of TSC is often clinically easy, but in infancy the most characteristic manifestations have not yet appeared. By far the most powerful diagnostic tool is neuroimaging by computed tomography (CT) or MRI. CT is abnormal in 89% of patients. It shows subependymal calcified nodules, especially in the region of the foramen of Monro; cortical or subcortical areas of decreased attenuation that correspond to tubers and may be associated with widening of the adjacent gyrus; focal areas of increased attenuation corresponding to calcified tubers; in some patients ventricular dilatation or cortical atrophy or both; and occasionally cerebellar calcification. Gyriform calcification simulating that in Sturge–Weber syndrome may occur (Wilms et al. 1992). Contrast enhancement is useful if a giant cell astrocytoma is suspected as these take up contrast in 80% of patients.

MRI may not show all the calcified lesions well, but does show cortical and subcortical tubers much better than CT. They present as high signal areas in T2-weighted sequences. These areas are generally much more numerous than hypodense areas evidenced by CT and are located in the cortex (Roach et al. 1991). They vary in number and localisation, and there is some relationship between the number and localisation of tubers and cognitive development and neuropsychological findings (Shepherd et al. 1995; Goodman et al. 1997; Bozzao et al. 2003). Although there is no strict correlation between neurodevelopmental difficulties and the number or density of tubers detected by imaging, there is a trend for patients with more tubers to have more cognitive or behavioural disturbances, and frontal and parietal locations may be more closely related with autism and intellectual disability (Curatolo 2003; Ridler et al. 2004). Deep white matter cystic abnormalities have been rarely reported (Canapicchi et al. 1996). Radial bands or wedge-shaped areas extending from ventricle to cortex or to a cortical tuber (Braffman et al. 1992) are composed of clusters of heterotopic cells and are indicative of a disorder of migration associated with abnormal cell differentiation. According to Gomez et al. (1988), a diagnosis of cerebral TSC can probably be discarded if both CT and MRI are negative for cerebral abnormalities.

The EEG is of interest to better define the type of epilepsy associated with TSC. Atypical hypersrrhythmia, often asymmetrical, is present in one-third of patients early in the course of the disorder, when epileptic spasms are present. Focal signs are present in at least 40% of tracings (Yamamoto et al. 1987). In later childhood, focal paroxysms or bilateral slow spike–wave complexes may be found.

**Management of TSC**

Genetic testing should be offered for family counselling or when diagnosis is doubtful. Careful examination of both parents including Wood’s lamp inspection of the skin should be performed, especially clinical and ophthalmological assessment. The assessment also includes: a search for possible cases in the family, renal ultrasonography and brain MRI. In the usual case of an isolated patient without family history of the disease, a favourable genetic prognosis can be given with very few reservations, provided both parents have been carefully examined and have been found not to have any cutaneous, neurological or visceral features of the disease. Even
so, a small proportion of such cases (<1%) may be missed (Roach and Sparagana 2004). Prenatal diagnosis can be suspected on the basis of a fetal ultrasound examination showing cardiac rhabdomyomas or polycystic kidneys. A prenatal head MRI after the 20th week of gestation can identify large cortical tubers.

Krueger and Northrup (2013), on behalf of the International Tuberous Sclerosis Complex Consensus Conference, provided recommendations on surveillance and management. MRI of the brain every 1–3 years is advised before 25 years of age to monitor for new occurrence of subependymal giant cell astrocytoma (SEG). Surgical resection or shunt should be performed for acutely symptomatic SEG. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEG.

Regular evaluation should be performed for TSC-associated neuropsychiatric disorders (e.g. ASD, attention-deficit–hyperactivity disorder).

Parents should be educated to recognise infantile spasms in infants. EEG monitoring is recommended every month for the first 6 months and then every 6–8 weeks unless there are other abnormalities (Curatolo et al. 2012). Also prophylactic management of patients based on early EEG changes has been shown to improve cognition and seizure control with lesser need for polypharmacy in the long run (Jóźwiak et al. 2011). Further prospective studies, focusing on the overall efficacy of prophylactic treatment are still needed.

MRI of the abdomen should be performed every 1–3 years to assess for the presence of angiomyolipoma and renal cysts. Renal function then (including determination of glomerular filtration rate [GFR]) and blood pressure should be assessed at least annually. Embolisation followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute haemorrhage. For asymptomatic, growing angiomyolipoma measuring larger than 3cm in diameter, treatment with an mTOR inhibitor is recommended (Krueger and Northrup 2013).

Pulmonary function testing and chest high resolution CT, is indicated, in patients at risk of developing lymphangioleiomyomatosis, typically females 18 years or older. mTOR inhibitors may be used in moderate to severe or rapidly progressing lung disease.

A detailed skin examination should be performed annually. A detailed dental examination should be performed regularly and panoramic radiographs by age 7 years if not performed previously, in order to screen for symptomatic or deforming dental lesions, oral fibromas and bony jaw lesions.

Fetal echocardiography is used to detect individuals at high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound. Echocardiograms should be performed in children, especially before age 3 years until regression of rhabdomyomas. Electrocardiograms should be obtained in all ages to assess for underlying conduction defects. A complete ophthalmological evaluation including dilated fundoscopy should be performed to assess for retinal lesions and visual field deficits (Krueger and Northrup 2013).

There is no specific treatment for the disease itself, but several of its manifestations are amenable to therapy. Antiepileptic drugs should be given for seizures, and infantile spasms may justify adrenocorticotropic hormone (ACTH) or steroid treatment. Vigabatrin is particularly effective as a first-line drug in the treatment of infantile spasms due to TSC, and to a lesser extent for treatment of focal seizures (Curatolo and Seri 2003).

Removal of a large tuber may be successful in controlling seizures in some patients. Determination of the existence of a single epileptogenic tuber is a prerequisite. This may be achieved by careful EEG and imaging studies (Lachwani et al. 2005). A large tuber containing a nidus of calcification is most likely to be an epileptogenic tuber (Koh et al. 2000; Karenfort et al. 2002). The use of alpha-methyltryptophan, which appears to fixate electively on active tubers, was suggested by one group (Chugani et al. 1998). In this study authors were able to effectively differentiate the epileptogenic tubers from nonepileptogenic tubers using alpha methyl tryptophan (AMT) positron emission tomography (PET) as opposed to glucose metabolism PET scan, which shows cortical areas of hypometabolism corresponding to the location of all the tubers – epileptogenic and nonepileptogenic. AMT PET has been found to be useful in patients with multifocal EEG abnormalities to localise effectively and resect the epileptogenic tuber for a more favourable seizure outcome. Seizure freedom rates may be much lower if tubers are nonlocalisable by AMT PET (Kagawa et al. 2005).

Further confirmation of the epileptogenic tuber and extent of the resection may involve invasive evaluation with depth electrodes (Stereo-EEG) and electrocorticography (ECoG) (Shahid 2013; Arzimanoglou and Kossof 2016). Resection of epileptogenic tubers alone leaving the peritubular cortex intact has been reported with good results (Mohamed et al. 2012). However, a resection of both the tuber and the perituberal cortex results in a more favourable long-term outcome. It remains to be determined whether resection of an epileptogenic tuber may be associated with ‘activation’ of another lesion that could lead to persistence of seizures (Karenfort et al. 2002).

Epileptogenic tubers located in eloquent cortex can be safely removed without any long-term deficits, thus proving the nonfunctionality of these tubers (Moshe et al. 2010). In 2006, Franz et al. showed that rapamycin, an inhibitor of mTOR, can inhibit the growth of astrocytomas in TSC. Further reports of success of rapamycin (sirolimus) and everolimus in renal angiomyolipoma and lymphangioleiomyomatosis have been published (Wienecke et al. 2006; Bissler et al. 2008). Everolimus, an orally administered mTOR inhibitor, is the first pharmacological therapy approved for the treatment of TSC. The therapeutic efficacy and safety of everolimus have been demonstrated in multicentre, international, randomised, double-blind,
placebo-controlled trials. These studies continue in their extension phases with the goal of establishing the long-term safety and efficacy profile of everolimus in patients with TSC. Targeted systemic therapies such as everolimus are particularly useful in that they treat the multiple manifestations of TSC and offer patients both a means of symptom relief and a treatment alternative to invasive surgical procedures (Franz 2013).

**CLASSIC LINEAR NEVUS SYNDROME**

In its complete form, Classic Linear Nevus or Schimmelpenning-Feuerstein-Mims Syndrome includes a cutaneous nevus with neurological and eye abnormalities. The skin lesion may be of several types. One typical appearance is that of the sebaceous nevus of Jadassohn. This lesion usually involves the head or face, and may be visible at birth or in infancy or become evident only after a few years (Clancy et al. 1985). It is a slightly raised, yellow-orange, smooth, linear plaque that abuts the midline of the forehead, nose or lips and often involves the scalp. It tends to become darker and verrucous as years pass. Early in life there is mainly acanthosis and little pigment, and sebaceous glands are often not prominent. Later, sebaceous glands proliferate, and apocrine glands may be located aberrantly throughout the thickness of the skin.

A second type of nevus is the verrucous nevus, which is formed of discrete papules, slightly darker than the surrounding skin, with a linear organisation. Such nevi are more often located on the body and less on the face than the sebaceous nevus, and histologically there is only acanthosis and hyperkeratosis with abnormal dermis (Prensky 1987). It seems that either type of nevus may be associated with neurological abnormalities (Clancy et al. 1985; Menascu and Donner 2008), although most skin lesions are isolated. Associated cutaneous abnormalities such as ichthyosis, acanthosis nigricans, haemangiomatis and café-au-lait spots are frequent, and linear nevus overlaps with other neurocutaneous syndromes with proliferative skin and subcutaneous tissue lesions (see section on Related Syndromes with Proliferative Skin and Subcutaneous Tissue Lesions).

Neurological manifestations associated with both types of nevi consist of intellectual disability, seizures, cranial nerve palsies, hydrocephalus and asymmetrical macrocephaly (van de Warrenburg et al. 1998; Menascu and Donner 2008). Seizures are often focal, but infantile spasms have been observed in four of 11 patients in one series (Vigevano et al. 1984).

From a pathological point of view, the most common brain abnormalities are disorders of proliferation and migration (Prayson et al. 1999). Hemimegalencephaly (Pavone et al. 1991; Boer et al. 2007) is frequent and may be associated with hemihypertrophy of the ipsilateral face and body. Hamartomatous tumours were present in several patients (Clancy et al. 1985). Destructive lesions such as porencephaly have also been found (Baker et al. 1987; Prensky 1987) and may be of vascular origin as arterial aneurysms, arteriovenous malformations and abnormal venous return have been reported (Dobyns and Garg 1991). Similar lesions have been found in the spinal cord. Other CNS abnormalities include arachnoid cysts, subtotal cerebellar agenesis, and callosal agenesis with Dandy–Walker malformation (Dodge and Dobyns 1995).

The most common eye abnormalities are dermoids or epidermoid of the conjunctiva and colobomas of the iris, choroid, retina or optic nerve. Enlargement of the orbit and of the greater wing of the sphenoid on the side of the nevus may be present. Familial cases are rare (Meschia et al. 1992). The diagnosis may be difficult early on in people without visible nevus. MRI, with diffusion-tensor imaging, is the most sensitive study for diagnosing hemimegalencephaly, which is present in about 50% of children with epidermal nevus syndrome. The most common imaging findings are hypertrophy of one hemisphere, usually on the same side as the nevus, with enlargement of the ipsilateral ventricle, and pachygyria, polymicrogyria or nodular heterotopias (Kruse et al. 1998; Mori 2004). Such an image is consistent with pathological reports of hemimegalencephaly or other migration disorders.

The EEG usually shows paroxysmal activity over the involved hemisphere, sometimes with a hypsarhythmic pattern. The prognosis is usually serious but mild cases exist with only seizures or mild learning difficulties. Treatment is symptomatic.

Epilepsy, which develops in most children with hemimegalencephaly, is typically refractory to medical management and resective epilepsy surgery (hemispherotomy) remains the treatment of choice (Vigevano et al. 1989; Shimizu 2005; Di Rocco et al. 2006; Luders and Schuele 2006; Salamon et al. 2006; Loddenkemper et al. 2008). Removal of the cutaneous lesion is possible in some patients.

The occurrence of the syndrome is sporadic. Epidermal nevus can result from somatic mosaicism for mutations in the FGFR3 gene (Hafner et al. 2006), the PIK3CA gene (Hafner et al. 2007), and the RAS genes (KRAS, HRAS and NRAS). Linear nevus syndrome can be caused by postzygotic somatic mutation in the HRAS gene on chromosome 11p15, the KRAS gene on chromosome 12p12, or the NRAS gene on chromosome 1p13 (Groesser et al. 2012; Hafner et al. 2012; Levinsohn et al. 2013).

Other neurocutaneous syndromes with presence of nevi are reported in the literature:

- **CHILD syndrome** is an acronym for an X-linked dominant disorder characterised by congenital hemidysplasia with ichthyosiform erythroderma and limb defects (Happle
et al. 1980). It has been found to be caused by mutation in the gene encoding NSDHL (König et al. 2000).

- **SCALP syndrome**, which includes sebaceous nevus syndrome, CNS malformations (including hemimegalencephaly), aplasia cutis congenita and limbal dermoid, with pigmented nevus (giant congenital melanocytic nevus) and neurocutaneous melanosis (Lam et al. 2008).

- **CLOVE syndrome**, congenital lipomatous overgrowth, vascular malformations, and epidermal nevi. There is evidence that CLOVE syndrome can be caused by somatic mosaicism for postzygotic activating mutations in the PIK3CA gene (Sapp et al. 2007; Kurek et al. 2012). Patients were initially mistakenly identified as having Proteus syndrome. The acronym was later expanded to CLOVES to include the association with scoliosis and skeletal and spinal anomalies (Alomari 2009).

**RELATED SYNDROMES WITH PROLIFERATIVE SKIN AND SUBCUTANEOUS TISSUE LESIONS**

**ENCEPHALOCRANIOCUTANEOUS LIPOMATOSIS (HABERLAND SYNDROME) AND OCULOCEREBROCUTANEOUS SYNDROME (DELLLEMAN SYNDROME)**

Encephalocraniocutaneous lipomatosis (Haberland Syndrome) and oculocerebrocutaneous syndrome (OCCS; Dellemann Syndrome) are rare, closely related, apparently sporadic syndromes characterised by microcephaly, lipodermoids involving the conjunctiva, sclera or eyelids, and lipomatous swelling over the cranium or face along with skin lesions like alopecia. About two-thirds of the patients have normal development or mild intellectual disability only, and half of them have seizures. Porencephalic cyst and intracranial and/or intraspinal lipoma are the most common CNS abnormalities, followed by enlargement of the lateral ventricles, arachnoid cysts, widening of the subarachnoid spaces, dysplastic cortex, and corticopial calcifications, thinning of the corpus callosum and leptomeningeal angiomatica. Aortic coarctation, progressive bone cysts and jaw tumours may be associated (Pascal-Castroviejo et al. 2005b; Moog et al. 2005, 2007; Moog 2009). The condition may share some clinical manifestations with the Proteus syndrome (McCall et al. 1992).

**PROTEUS SYNDROME**

This term applies to a complex hamartomatous syndrome consisting of partial gigantism, asymmetry of the limbs, linear verrucous and intradermal nevi, shagreen patches and variable combinations of lymphangiomas, haemangiomas, macrocephaly and hyperostoses. Plantar skin hyperplasia (the so-called mocassin lesion) is a frequent and useful diagnostic feature (Nguyen et al. 2004). Epibulbar dermoids, colobomas, glaucoma and retinal detachment can occur. Some patients may have intellectual disability. Hemimegalencephaly is frequent (Griffiths et al. 1994). The deformities resulting from the syndrome can reach extreme proportions, as in the case of Joseph Merrick, the so-called Elephant Man. The disease is still commonly misdiagnosed as neurofibromatosis.

As the name implies, the Proteus syndrome has a very variable expression (Cohen 2014). Visceral tumours may occur (Gordon et al. 1995). Most proven cases to date have been sporadic. There is evidence that Proteus syndrome is associated with a somatic activating mutation in the AKT1 gene, proving the hypothesis of somatic mosaicism and implicating activation of the PI3K–AKT pathway in the characteristic clinical findings of overgrowth and tumour susceptibility in this disorder (Lindhurst et al. 2011).

The diagnosis is difficult as the limits of the syndrome are not well defined. Turner et al. (2004) found that among 205 patients described in the literature, only 97 (43%) met strict criteria. In a review, Cohen (2014) provided revised diagnostic criteria, noting that the presence of cerebriform connective tissue nevus is a major diagnostic feature, although it is not found in all patients. Patients whose conditions do not meet such criteria are sometimes termed ‘Proteus-like syndrome’ (Zhou et al. 2000) and some of them were associated with germline and tissue-specific somatic mutations in the PTEN gene, responsible for Cowden or Bannayan–Riley–Ruvalcaba syndrome (PTEN hamartoma syndromes).

**OTHER SYNDROMES WITH TISSUE PROLIFERATION – PTEN HAMARTOMA TUMOUR SYNDROMES**

Cowden syndrome is characterised by the association of various skin lesions especially facial trichilemmomas and other cutaneous abnormalities, with other hamartomas that may include intestinal polyps. In childhood, clinical features include macrocephaly, scrotal tongue and mild-to-moderate intellectual disability, while cutaneous tumours and other characteristic features appear only later in life (Hanssen and Fryns 1995). Busch et al. (2013) concluded that, contrary to previous reports suggesting an association with intellectual disability, the mean intellectual intelligence quotient was average, with a broad range of function. Patients have a risk for thyroid, breast and endometrial cancers. Approximately 80% of cases are due to germline mutations of the tumour suppressor PTEN gene (Blumenthal and Dennis 2008). The most striking neurological feature is the cerebellar hamartomaticous hyperplasia of Lhermitte–Duclos disease, also due to mutations in the PTEN gene, which in fact is part of the spectrum of Cowden syndrome (Perez-Nunez et al. 2004; Tan and Ho 2007).
Chapter 4  Neurocutaneous Diseases and Syndromes

Bannayan–Riley–Ruvalcaba syndrome (BRRS) is associated with PTEN gene mutations in some patients (Hendricks et al. 2003). In its complete form it presents with macrocephaly, intestinal polyposis, lipomas, angiomas, mucocutaneous pigmentation and developmental delay or intellectual disability.

Lachlan et al. (2007) concluded that the BRRS and Cowden syndrome represent one condition with variable expression and age-related penetrance, which is common in tumour suppressor disorders, and suggested that it is not helpful to split PTEN related disorders into separate clinical syndromes. Pilarski et al. (2011) tried to describe clinical features that predicted a PTEN mutation and Tan et al. (2011) developed a clinical scoring system for selection of patients for PTEN mutation testing.

NEUROCUTANEOUS SYNDROMES WITH PROMINENT VASCULAR COMPONENTS

Several syndromes are characterised by the association of cutaneous abnormalities and vascular malformations of the CNS. The type of vascular abnormalities is widely variable, and multiple associated anomalies are common.

STURGE–WEBER SYNDROME

Sturge–Weber syndrome (SWS) is by far the most frequent of the disorders of this group. In its complete form it consists of a venous angioma of the leptomeninges, ipsilateral flat facial angiomatous nevus (‘port-wine stain’) (Fig. 4.10) and chorioid angioma. An identical pial angioma may be present in isolation or in association with chorioidal angioma without facial nevus in up to 13% of patients (Gomez and Bebin 1987; Roach 1992; Pascual-Castroviejo et al. 1993; Comi 2015). Such cases, for all practical purposes, should be regarded as belonging to the same syndrome. However, some of these cases may represent errors of diagnosis (e.g. cases of the syndrome of intracranial calcification with coeliac disease). On the other hand, patients who have facial nevus without CNS involvement with or without glaucoma are common (Roach 1992).

A recent study showed that 23 of 26 patients with SWS were positive for the c.548G→A somatic mutation in GNAQ gene, in either port-wine–stained skin or brain tissue. The GNAQ gene on chromosome 9q21, encodes Gαq, a member of the q class of G-protein alpha subunits that mediates signals between G-protein–coupled receptors and downstream effectors. The variant is predicted to result in the amino acid substitution p.Arg183Gln (Shirley et al. 2013). The same mutation causes isolated port-wine birthmarks, thus linking pathogenically both the non-syndromic with the syndromic forms of the birthmarks.

Cutaneous Manifestations in SWS

The nevus flammeus (‘port-wine stain’) almost always lies above the level of the palpebral fissure involving the upper eyelid or frontal region or both. Frontal lesions close to the midline are more commonly associated with anteriorly located pial lesions and more external frontal involvement with the more frequent occipitoparietal angiomas, but the correlation between the extent and location of the nevus and that of the pial angioma is poor. In a survey of 310 patients, Tallman et al. (1991) found neurological or ophthalmological involvement in 6% of those with unilateral and 24% of those with bilateral nevi in the territory of the first two divisions of the trigeminal nerve (only three patients had isolated involvement of the second division). These figures are likely to be underestimates as no imaging was performed. Sujansky and Conradi (1995a, b) computed a frequency of between 8% and 33% from a review of the literature. Some children have bilateral nevi with unilateral pial involvement (Gomez and Bebin 1987). Bilateral meningeal angiomas may coexist with either unilateral or bilateral facial nevi. Pascual-Castroviejo et al. (1993) found 13 patients with bilateral nevi in their 40 patients with SWS.
In only three of these was the CNS angioma bilateral.Rare instances of people who have angioma contralateral to the nevus flammeus are on record (Widdess-Walsh and Friedman 2003). Angiomas not uncommonly may extend beyond the face and involve the neck, trunk or limbs on one or both sides.

The intracranial angioma is limited to the pia mater that contains dilated and tortuous venules that may form several layers in the subarachnoid space but rarely enter the brain. The calcifications lie in the cortex underlying the angioma and subcortical white matter, tending to appear deeply at first and then extending toward the surface (Comi 2003; Thomas-Sohl et al. 2004). Localised or unilateral brain atrophy is virtually constant. In one severe case, four-layer microgyria was found underlying the angioma, indicating a prenatal origin of cortical damage (Simonati et al. 1994). Localised atrophy of prenatal origin (Portilla et al. 2002) also indicates the possible early repercussions of the angioma on cerebral development.

**Neurological Manifestations in SWS**

Seizures are the major neurological manifestation of SWS, occurring in 75–90% of patients (Gomez and Bebin 1987; Sujansky and Conradi 1995b; Arzimanoglou and Aicardi 1992). They usually have their onset in the first months of life. They are generally focal motor in type and are often prolonged in episodes of status epilepticus. Generalised seizures and even myoclonic and tonic seizures or infantile spasms can occur (Chevrie et al. 1988; Arzimanoglou and Aicardi 1992; Ewen et al. 2007; Barbagallo et al. 2009). Many patients have frequent and repeated seizures (Oakes 1992), but some children have only an occasional seizure, and approximately half the patients in one series responded relatively well to drug therapy (Arzimanoglou and Aicardi 1992).

The EEG shows reduced background amplitude over the angioma in a majority of patients. Associated paroxysmal abnormalities are often found on the involved side, although this may be a late sign. Generalised bisthronynchronous discharges can be present in patients with unilateral pial lesions (Chevrie et al. 1988; Ewen et al. 2007) but should not be considered as a contra-indication when considering surgery. Paradoxical predominance of the paroxysmal features on the normal side may be seen. According to Jansen et al. (2004), abnormally small amplitude of the beta rhythm following administration of benzodiazepines may help to localise the area of parenchymal damage. Ewen and colleagues (2009) reported use of quantitative EEG to screen infants with facial port-wine birthmark.

Hemiplegia occurs in at least one-half of patients and is localised to the side opposite the facial nevus, except in a very few patients who probably have bilateral disease (Terdjman et al. 1990). Hemiplegia usually first appears after an episode of seizures and may become more severe with the recurrence of seizures. Hemianopia is virtually constant, isolated or in association with hemiparesis.

Transient hemiplegias not following an epileptic attack and sometimes accompanied by migraine-like headache are observed in many patients with SWS (Arzimanoglou and Aicardi 1992; Jansen et al. 2004). These hemiplegic episodes are apparently not of epileptic nature and may be a consequence of vasomotor disturbances within and around the angioma (Terdjman et al. 1990). Migraine-like episodes can also occur in the absence of hemiplegia (Taddeucci et al. 2005).

Intellectual disability is present in about 40% of the patients and in 75% of those with seizures. It does not occur in patients without epilepsy and is more common and more severe in bilateral forms (Gomez and Bebin 1987; Sujansky and Conradi 1995b). In many patients, there appears to be a definite regression of cognitive abilities parallel to the repetition and severity of the seizures.

Reesman and colleagues (2009) reported that significant hemiparesis correlates with general adaptive dysfunction. This examination finding may be useful for identifying children in need of additional interventions and eventually surgery.

Intracranial haemorrhage is not a feature of SWS. However, elevated spinal fluid protein is commonly found (Skoglund et al. 1978) and may correspond to minimal haemorrhage from the angioma. This interpretation is also consistent with the occasional occurrence of hydrocephalus (Fishman and Baram 1986), as observed also in a personal case, or with protein exudation from the angioma. Macrocephaly not due to hydrocephalus has also been reported (see Cohen 2003).

Glaucoma is present in 30–48% of SWS patients (Sujansky and Conradi 1995b), and 50% have choroidal angioma that may sometimes be visible with the ophthalmoscope. The glaucoma may be the consequence of overproduction of aqueous fluid by the choroidal angioma, or else exudate from the lesion may block the angle.

**Imaging Features in SWS**

MRI is the investigation of choice as it allows a relatively good visualisation of the pial angiomatosis and its limits. With gadolinium enhancement, the pial angioma can be clearly made out (Lipski et al. 1990; Sperner et al. 1990; Benedikt et al. 1993; Vogl et al. 1993). This may permit a preclinical diagnosis of the SWS in patients with an apparently isolated facial nevus, and may indicate the extent of the angioma and the presence or absence of contralateral involvement (Fig. 4.11). High resolution techniques of three dimensional magnetic resonance angiography may show a blush at the site of the angioma, and MRI may demonstrate advanced myelination at this locus. Perfusion MRI may permit an earlier diagnosis and more precise delineation of parenchymal abnormalities (Lin et al. 2003; Evans et al. 2006), and together with spectroscopy can determine the correlations with clinical symptoms and help surgery planning (Lin et al. 2006). Magnetic resonance spectroscopy and susceptibility-weighted imaging may detect abnormalities not seen on standard MRI with contrast (Batista
et al. 2008; Hu et al. 2008). A recent series of 15 participants demonstrated infratentorial involvement in 40% and suggested that antibody drug conjugate analysis of normal-appearing white matter may reveal distant abnormalities and serve as a useful biomarker of brain tissue injury (Arulrajah et al. 2010). A better definition of the venous abnormalities might also be obtained with blood-oxygen-level-dependent (BOLD) magnetic resonance venography (Mentzel et al. 2005).

CT is a powerful tool for the detection of calcium and can often show its presence in infants of only a few months of age or even in neonates. CT also clearly demonstrates atrophy of the brain, enlargement of the choroid plexus on the side of the pial angioma, and abnormal veins draining into the deep venous circulation (Terdjman et al. 1990). MRI shows calcification less well than CT. Enhancement seen on CT may not represent opacification of the pial angioma but rather cortical injection similar to that occurring in postconvulsive hemiplegia, and it may disappear and reappear with the occurrence and disappearance of seizures (Terdjman et al. 1990; Shin et al. 2002).

Plain skull X-rays show the classic ‘tramline’ calcification most frequently in the parieto-occipital area. Although this has occasionally been detected in the neonatal period, it is often a late sign and may be absent even in adolescents. Angiography is not usually indicated. It does not show the angioma but demonstrates lack of superficial cortical veins, nonfilling of dural sinuses and abnormal, tortuous veins that course toward the ventricle and vein of Galen system.

Examination with PET or single photon emission computed tomography (SPECT) shows hypometabolism or marked underperfusion in the area of the pial angioma and may help to detect latent angioma (Chugani et al. 1989). Ichinose et al. (2003) found in one case decreased blood flow and glucose hypometabolism of the involved hemisphere as shown by SPECT and fluorodeoxyglucose PET respectively on the one hand, and accumulation of 11C-methionine thought to result from gliosis on the other.

**SWS: Diagnosis and Course**

The diagnosis of Sturge–Weber syndrome is usually straightforward. However, in mild cases and in children who have not had seizures with a facial nevus that has been present from birth it may be very difficult to know whether a pial angioma is associated. MRI after enhancement with gadolinium or with water diffusion studies can answer this but whether it is justified is difficult to decide, as the frequency of cases of cutaneous angioma without seizures is not known. A few cases of TSC mimicking SWS with leptomeningeal enhancement and enlargement of the choroid plexus are on record (Kremer et al. 2005). The differential diagnosis includes other causes of cortical calcification and atrophy. The syndrome of cortical calcification, epilepsy and coeliac disease (Gobbi et al. 1988) is described below. Other causes of calcification mimicking the ‘tramline’ type include neurofibromatosis and rare cases of TSC (Wilms et al. 1992).

The neurological defects seen in SWS are probably the consequence of blood stagnation, hypoxaemia and impaired neuronal metabolism (Comi 2003). The hypoxaemic effects are exaggerated by the increased metabolic rate resulting from epileptic seizures, and probably also by vasomotor changes and thrombotic phenomena that take place in and about the pial lesion (Aylett et al. 1999). Such a mechanism may explain the progressive aggravation of damage all too often.

![Figure 4.11](image-url) Six-year-old boy with Sturge–Weber syndrome. (a) T2-weighted and (b) post-contrast T1-weighted axial MRI images showing mild temporal atrophy and lepto-meningeal enhancement. Note also enhancement of the left choroidal angioma (b, white arrow).
observed in these patients. It would also account for the beneficial effect of early surgery, preventing this cascade of ill effects.

A common embryological origin from the neural crest of the vascular bed of the leptomeninges and optic cup probably explains the Sturge–Weber association. The disease is sporadic. Only a few, doubtful, familial cases are on record, and the genetic prognosis is good.

The natural course of SWS depends on the presence, persistence and resistance to treatment of the seizures (Oakes 1992). In some patients, the disorder may remain static after marked atrophy has developed, and the seizures may subside or be relatively easily controlled. Onset of seizures before 1 year of age, a hypersarrhythmic EEG pattern, the occurrence of episodes of status and bilateral involvement predict an unfavourable spontaneous outcome. Cognitive and behavioural development is quite variable. It may be good, especially if control of the seizures is obtained. Intractable epilepsy is an indication for surgical treatment.

Differential Diagnosis

Children with epilepsy and intracranial calcification may have an incomplete form of SWS. However, Gobbi et al. (1988) have described a distinctive syndrome of epilepsy with intracranial calcification associated with coeliac disease different from SWS. The syndrome features unilateral images of calcification, similar to those in SWS, whose origin is not known. Calcification is often but not always occipital and is not necessarily bilateral. There is usually no detectable atrophy associated with the calcification and no abnormalities of the cortical veins or choroid plexus, but hypodensity of the white matter is often seen in the vicinity of calcified areas (Gobbi 2005). The pathology of the syndrome is poorly known. In a few patients, vascular abnormalities reminiscent of SWS in the form of foci of angiomatous venous dilatation were reported (Bye et al. 1993); they were not found in another case (Toti et al. 1996). The epilepsy is sometimes associated with progressive cognitive and epileptic deterioration. This syndrome may not be homogeneous. It is characterised by variable types of seizures that may have a severe course but may also occur infrequently and be controllable by drug therapy. The patients may have full-blown coeliac disease; more often, the disorder lacks digestive manifestations and the diagnosis then rests on jejunal biopsy showing typical mucosal atrophy. In some cases, the biopsy may give normal results, so the ultimate diagnostic criterion in such patients is the presence of antibodies against glia is found in the blood. An immunological mechanism seems likely and is supported by the high incidence of certain HLA groups (HLA DQ2 and DQ8). Although calcification resembles that resulting from folic acid deficiency, administration of this compound has no positive effect. The treatment is suppression of gluten-containing foods, which has to be maintained throughout life. The effect of the diet on epilepsy is variable and may depend on the precocity of its use (Gobbi 2005). When early, there seems to be a positive effect on seizures.

A few rare vascular syndromes may be only variants of SWS. These include cases of SWS associated with macrocephaly and hydrocephalus (Fishman and Baram 1986), which have been attributed to abnormal venous drainage with resulting intracranial hypertension. A syndrome of bilateral facial nevi, macrocrania and anomalous venous return through superficial veins is regarded by some authors (Shapiro and Shulman 1976; Orr et al. 1978) as probably different from SWS. Association with bilateral lymphatic/venous malformation has been reported (Ramli et al. 2003). Klippel–Trenaunay syndrome, which involves mainly the peripheral vascular system, may be associated with cranial anomalies (Williams et al. 1992).

Treatment in SWS

Treatment is mainly directed against the seizures, and an aggressive antiepileptic regimen should be established from the first seizure. Control can be obtained with drugs in about half the patients, even in those with early-onset seizures (Arzimanoglou and Aicardi 1992). Arrest of status epilepticus is of utmost importance, as hemiplegia is often postconvulsivel.

In patients with uncontrollable epilepsy, especially in infants, functional hemispherectomy, or classic occipital or parietal lobectomy or resection of the angiomatous area could render the patient seizure-free and possibly prevent cognitive deterioration. Hemispherotomy has also given very good results for the control of seizures (Schrupp et al. 2006). It is indicated for uncontrollable seizures when fine hand movements are absent (Roach et al. 1994) although some authors have advocated it in nonparalytic severe cases (Kossoff et al. 2002). Arzimanoglou et al. (2000) reported excellent control of seizures after hemispherectomy but less favourable results after lobar or incomplete resections. Kossoff et al. (2002) reviewed 32 patients of hemispherectomy for SWS from the world literature; satisfactory control of seizures was obtained in about 26 of these patients without significant increase in hemiplegia. The series by Bourgeois et al. (2007) of 27 patients found that 11 out of 19 (58%) with focal resections became seizure-free, mostly if a complete resection was performed. A review of 55 individuals with SWS indicated that early surgical treatment controlled the seizures but other neurological problems such as hemiparesis and intellectual deficits showed a less satisfactory response. Early onset of seizures and poor response to medical treatment, bilateral cerebral involvement and unilateral severe lesions were indicative of a poor prognosis (Pascual-Castroviejo et al. 2008) fully justifying early referral to paediatric epilepsy teams with experience in epilepsy surgery.

Even bilateral cases may be amenable to surgery provided the seizures consistently originate from one side as shown by
clinical seizure features, repeated EEGs and possibly functional imaging techniques (Tuxhorn and Panneck 2002; Schropp et al. 2006). Clinical experience favours early intervention, preferably in the first year of life, if frequent seizures or status epilepticus occur. However, the results on neurodevelopment may be disappointing even with early control of epileptic activity.

A neuropathological series of six patients after hemispherectomy revealed that all patients either had evidence of polymicrogyria or focal cortical dysplasia type I (Maton et al. 2010). Another series of two adult surgical patients reported association with focal cortical dysplasia type IIa (Murakami et al. 2012). Therefore, cortical malformation may be common in patients with SWS and intractable epilepsy intractable seizures, contributing to the severity of their epilepsy. Corpus callosotomy (Rappaport 1988) proposed as an alternative to hemispherectomy is finally limited to a minority of cases in contemporary clinical practice.

The possibility of preventing the occurrence of seizures by early antiepileptic treatment has been studied by Ville et al. (2002). Although they found a significant, if slight, difference favouring the group treated with phenobarbital over controls, the small number of patients and the heterogeneity of cases renders a conclusion difficult in view of the uncertainties about long-term side effects of such therapy.

Some authors studied mostly in a retrospective manner the safety and efficacy of low-dose aspirin and reported positive results (Udani et al. 2007; Lance et al. 2013). More studies are needed to establish whether all patients with SWS should be on low-dose aspirin and how long they should stay on it. A survey indicated that either triptans or daily preventive medication can be used in case of migraines and may be helpful (Kossoff et al. 2007). However, the small sample size precluded any safety analysis, demonstrating that future prospective trials of both treatment options are needed.

Local treatment of the port-wine stain is psychologically important, and good results have been obtained with pulsed dye laser (Léauté-Lebrège et al. 2002).

**SYNDROME OF HAMANGIOMAS AND OTHER CARDIOVASCULAR DEFECTS (PHACES SYNDROME)**

PHACE or PHACES syndrome (Frieden et al. 1996) or Castroviejo syndrome II (Pascual-Castroviejo 1985; Pascual-Castroviejo et al. 1996, 2005a) is typically associated with a posterior fossa malformation, haemangiomas, arterial abnormalities, coarctation of the aorta, eye abnormalities and sternal maldevelopment. The angiomas are variably flat or tuberous, usually involve the face or neck, and may be multiple. They may appear only after birth. This syndrome predominates in girls (90%) and has a wide spectrum of manifestations that can involve many organs throughout the body (Metry et al. 2001, 2006). Rare cases have been familial.

Intracranial anomalies are the most common extracranial feature of PHACE syndrome (Bracken et al. 2011). The posterior fossa malformation usually resembles Dandy–Walker syndrome but hypoplasia of the vermis or of the whole cerebellum and unilateral absence of a cerebellar hemisphere may be found. Besides cerebellar hypoplasia diverse embryological abnormalities of the aortic arch and of cervical and especially extracranial and intracranial vessels, as well as cortical dysplasia, are often found (Pascual-Castroviejo et al. 1996). Intracerebral haemangiomas and neuronal migration anomalies may be present (Poindexter et al. 2007). The arteriovenous malformation of PHACE syndrome commonly involves the internal carotid artery and its embryonic branches, ipsilateral to the cutaneous hemangioma, with dysgenesis and abnormal arterial course the most commonly noted abnormalities (Hess et al. 2010). Patients can also present arterial occlusions and stenosis, persistent embryonic arteries and saccular aneurysms (Heyer 2008). In addition to posterior fossa CNS anomalies, supratentorial anomalies may be present, and this may correlate with significant clinical sequelae (Oza et al. 2008). Coarctation of the aorta and congenital heart disease, especially septal defects, are frequent.

Variable eye defects may include proptosis, ptosis, cataracts and retinal anomalies (Kronenberg et al. 2005). Involvement of visceral vessels may occur. A malformed sternum is often found. Many patients have intellectual disability or a borderline intellectual level. Vascular and cardiac complications may occur, and fatal cases are on record. Strokes are a possible manifestation (Drolet et al. 2006). Treatment of the haemangiomas with corticosteroids may be effective, and surgery may be required for correction of some of the congenital defects.

Metry et al. (2009) defined diagnostic criteria. Major and minor criteria were determined for cerebrovascular, structural brain, cardiovascular, ocular and ventral/midline defects. Definite PHACE requires the presence of a characteristic segmental hemangioma, or hemangioma 5cm on the face or scalp, plus one major criterion or two minor criteria. The group recognised that it may be possible to have PHACE syndrome with a hemangioma affecting the neck, chest or arm only or no cutaneous hemangioma at all.

**VON HIPPEL–LINDAU DISEASE**

Von Hippel-Lindau (VHL) disease consists of the association of retinal, cerebellar and spinal haemangioblastoma, pheochromocytoma, cysts or neuroendocrine neoplasms of the pancreas, renal cell carcinoma, and endolymphatic sac tumour (Joerger et al. 2005). Cutaneous involvement (hemangiomas) occurs only in some cases, thus VHL is not a neurocutaneous disease in a majority of patients. The condition is transmitted as a dominant trait with a penetrance...

The diagnosis is made in patients with at least two of the aforementioned manifestations, or in patients with a known family history or a pathogenic mutation and at least one of the manifestations stated above (Huson et al. 1986; Binderup et al. 2013).

The disease manifests usually after 10 years of age by acute eye complications, (e.g. haemorrhage, or by a posterior fossa syndrome) (Kreusel 2005). Pancreatic and renal cysts are asymptomatic and are detected by abdominal imaging in three-quarters of patients. Renal carcinomas and phaeochromocytomas (Opocher et al. 2005) should be detected early if conservative treatment is to be contemplated.

CNS haemangioblastomas are a cardinal feature of VHL disease and are the presenting feature in 40% of patients. Overall CNS haemangioblastomas occur in 60–80% with VHL (Maher et al. 2011). Neumann et al. (1992) found that 44% of gene carriers had haemangioblastoma, multiple in 42% and 44% of those with haemangioblastoma had retinal lesions. The retinal haemangioma has a characteristic appearance. About 20% of patients with retinal angioma develop neurological complications, and 40% of patients with cerebellar haemangioblastoma have VHL disease (Huson et al. 1986). Lonser et al. (2014) analysed the CNS hemangioblastoma burden in 225 patients with multiple haemangioblastomas in the cerebellum (45%), brainstem (7%), spinal cord (36%), cauda equina (11%) and nerve roots (0.3%). Increased tumour burden was associated with partial deletions in the VHL gene and male sex.

Although CNS haemangioblastomas tend to enlarge over time, they are benign tumours and some may be static for a number of years and hence removal of asymptomatic lesions is not usually indicated. The judicious treatment of symptom-producing haemangioblastomas, while avoiding unnecessary treatment of asymptomatic tumours that may not progress, can provide clinical stability.

Patients and at-risk relatives should have annual paediatric examinations and ophthalmological assessment from 5 years of age. From 5 to 14 years, annual plasma-metanephrine and plasma-normetanephrine tests, as well as annual hearing test. Between the ages of 8 and 14 years, CNS and abdominal MRI. After the age of 15 years tests should include: (1) annual ophthalmoscopy, (2) annual neurological examination, (3) every 2 years: MRIs of the CNS, including the inner ear, (4) annual ultrasound/MRI of the abdomen, (5) annual plasma-metanephrine, normetanephrine and chromogranin A tests, and (6) annual hearing examination (Binderup 2013).

Treatment is purely surgical (Vougioukas et al. 2006). The prognosis is dominated by the presence and size of tumours, both intracranial and intra-abdominal. Generally, the results of surgery for a single peripherally located cerebellar lesion are excellent, but surgical management of multicentric tumours and brainstem and spinal tumours can be challenging and patients can benefit from being treated in units with specialised experience and expertise in VHL disease. Stereotactic radiotherapy may be an alternative to conventional neurosurgery (Maher et al. 2011).

**HEREDITARY HAEMORRHAGIC TELANGIECTASIA (RENDU–OSLER–WEBER SYNDROME)**

Hereditary haemorrhagic telangiectasia (HHT) is a familial disorder, transmitted as an autosomal dominant trait, characterised by the presence of multiple dermal, mucosal and visceral telangiectasias associated with recurrent haemorrhage (Mei-Zahav et al. 2006; Govani and Shovlin 2009). The most common manifestations in children carrying a mutation include cutaneous and nasal telangiectasias, and pulmonary and hepatic arteriovenous malformations (AVMs); central nervous system AVMs (CAVMs) or CNS ischaemic lesions complicating pulmonary AVMs were found in 12–16% of children with a mutation (Giordano et al. 2006, 2013).

Hereditary haemorrhagic telangiectasia CAVMs are more likely to be multiple and have a tendency toward small size and cortical location. As such, they are often treated using a single-modality therapy (Woodall et al. 2014).

Due to the debilitating and potentially fatal effects of CAVM rupture and the lack of evidence regarding effectiveness of treatment for asymptomatic CAVMs, the International Guidelines for Diagnosis and Management of HHT recommended screening for them in all patients (including children in the first 6 months of life) with possible or definite HHT (Faughnan et al. 2011). However, this has been a subject of significant debate as most CAVMs never bleed and investigations and treatments carry risks (Govani and Shovlin 2009; Garg et al. 2014). Both family history and early clinical signs are important to prompt further diagnostic testing to avoid intracranial haemorrhage from CAVMs in children (Saleh et al. 2013).

The most common complication of HHT is epistaxis, which, however, is rarely severe before age 35 years. Neurological involvement includes the complications of right-to-left shunt through pulmonary arteriovenous fistulas, responsible for brain abscesses, and thrombosis associated with polycythaemia.

Spinal arteriovenous fistulas were found in infants and young children, whereas AVMs with a nidus were found only in adults in one large series (Krings et al. 2005). Given the lack of data regarding the true incidence and natural history of these lesions, the question is raised of whether spinal cord imaging should be incorporated into screening recommendations (Calhoun et al. 2012). Recurrent alternating hemiplegia has been reported (Myles et al. 1970). Two major genetic subtypes are known (HHT1 and HHT2) due respectively
to mutations in the genes of endoglin (ENG) and ALK1/ACVRL1, each gene accounting for approximately half the patients (Bayrak-Toydemir et al. 2006). These genes code for proteins that help maintain the integrity of vascular endothelium. Two minor genetic subtypes have been reported (Abdalla et al. 2005).

The cutaneous lesions may be hard to discover and should be looked for carefully, especially when pulmonary arteriovenous fistulas are present. Surgical removal or endovascular treatment of haemorrhage of otherwise functionally detrimental lesions is indicated, and regular surveillance for detection of tumours outside the CNS is essential. Treatment with bevacizumab may be promising (Flieger et al. 2006). Bevacizumab, which targets vascular endothelial growth factor, was shown to decrease both cardiac index and epistaxis duration in patients with HHT with severe liver involvement (Azzopardi et al. 2015).

**RARE NEUROCUTANEOUS SYNDROMES WITH PROMINENT VASCULAR COMPONENT**

Neurocutaneous syndromes of which vascular abnormalities are an important part are listed in Table 4.3. Several of these are genetically determined. Cutaneous involvement may not be a major feature, and neurological symptoms may be the presenting feature. In all cases of vascular abnormalities of the CNS it is important to make careful enquiries about possible other cases in the lineage. In cases with known genetic origin or where two instances of vascular malformation exist in the family, a thorough examination of all family members is in order. The exact nosological situation of several of these syndromes is unclear.

**SNUDDON AND DIVRY–VAN BOGAERT SYNDROMES**

Sneddon syndrome consists of the association of generalised livedo reticularis (livedo racemosa) with cerebrovascular accidents due to diffuse abnormalities of the small and middle arteries (Legierse et al. 2008). Two subtypes are recognised: one where antiphospholipid antibodies are present with other features of inflammation (Szmyrka-Kaczmarek 2005), and an idiopathic type (Mascarenhas et al. 2003) that may be familial (Petticrea et al. 1994; Lossos et al. 1995). The syndrome can be caused by a compound heterozygous mutation in the CECR1 gene encoding the ADA2 protein (one such family has been reported; Bras et al. 2014). The disorder is a cause of cerebrovascular accidents, mostly in young adults, with a few cases reported in children (Baxter et al. 1993; Wheeler et al. 1998). In Sneddon syndrome, which shares many features with the Divry–Van Bogaert syndrome (Stone et al. 2001) there is noncalcifying leptomeningeal and cortical angiomatosis with secondary white matter sclerosis. The two conditions appear to be closely related (Ellie et al. 1994).

**SYNDROMES WITH VARIOUS CUTANEOUS OR SUBCUTANEOUS TISSUE ANOMALIES**

Several of these syndromes feature vascular anomalies of a phakomatous type such as angiomas, ectatic veins or lymphangiectasias, in association with macrocephaly and/or CNS abnormalities. The syndrome of cutis marmorata telangiectatica is clearly heterogeneous and may be accompanied by neurological symptoms (Picascia and Esterly 1989; Garzon and Schweiger 2004; Hinek et al. 2008) and the association of recurrent hemiplegias mimicking alternating hemiplegia has been reported (Baxter et al. 1993). The syndrome of macrocephaly–cutis marmorata congenita is probably different and includes dysmorphism and brain malformations (Lapunzina et al. 2004; Nyberg et al. 2005). It is also referred as **megaencephaly-capillary malformation-polymicrogyria syndrome** (MCAP) (Conway et al. 2007; Mirzaa et al. 2012) and diagnostic criteria have been proposed by different authors (Martínez-Glez et al. 2010; Mirzaa et al. 2012; Papetti et al. 2012). Some cases of MCAP have been found to have somatic mutations in the PIK3CA gene (Riviè re et al. 2012).

Several syndromes associate neurological abnormalities with proliferation of subcutaneous tissues, and in some there is a tendency to the development of tumours. The distinction between rare syndromes such as **Riley–Smith**, **Bannayan–Zonana** and **Riwalca–Myhre syndromes** is difficult and may be to some extent artificial (Dvir et al. 1988; Gorlin et al. 1992). They are associated with mutations in the PTEN gene and patients present intracranial developmental venous anomalies (Tan et al. 2007).

Wyburn–Mason syndrome (also known as Bonnet–Dechaume–Blanc syndrome or congenital retinocephalofacial vascular malformation syndrome) consists of a complex vascular malformation including a retinal arteriovenous angioma associated with a unilateral arteriovenous malformation extending along the optic nerve and the optic tract all the way to the cerebral peduncles and sometimes as far as the ipsilateral cerebellar hemisphere (Gomez 1994; Lester et al. 2005). A facial periorbital angioma is often present. Rupture or thrombosis of the malformation is not rare, with ominous consequences (Rizzo et al. 2004).
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical features</th>
<th>Genetics</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Blue rubber bleb nevus syndrome</td>
<td>Subcutaneous, mucous and visceral angiomas (venous malformations). The most serious complication is abundant gastrointestinal haemorrhage. Rare cases of multiple cavernous angiomas of the CNS</td>
<td>S or AD</td>
<td>Kim (2000); Eiris-Puñal et al. (2002)</td>
</tr>
<tr>
<td>Klippel–Trenaunay syndrome</td>
<td>Large cutaneous hemangioma with hypertrophy of the related bones and soft tissues. The disorder clinically resembles Sturge–Weber syndrome and the two have been associated in some cases</td>
<td>S or AD</td>
<td>Baraitser and Shieff (1990); Maramattom et al. (2005)</td>
</tr>
<tr>
<td>Cobb syndrome (cutaneomeningospinal angiomatosis)</td>
<td>Cutaneous flat angioma and myelopathy due to spinal cord angioma in same metameric location</td>
<td>S</td>
<td>Shapiro and Shulman (1976); Fishman and Baram (1986); Prats Viñas et al. (2011)</td>
</tr>
<tr>
<td>Shapiro–Shulman syndrome</td>
<td>Bilateral facial nevi, abnormal venous damage of the brain, macrocephaly</td>
<td>S</td>
<td>Dobyns et al. (1987); Gorlin et al. (1992); Hendricks et al. (2003); Lachlan et al. (2007); Pilarski et al. (2011)</td>
</tr>
<tr>
<td>Bannayan–Riley–Ruvalcaba or Bannayan–Zonana or Riley–Smith or Ruvalcaba–Myhre–Smith syndrome</td>
<td>Macrophage, lipomatosis, cutaneous angiomas</td>
<td>PTEN gene</td>
<td>Garavelli et al. (2005); Lapunzina et al. (2004); Mirzaa et al. (2012); Rivière et al. (2012)</td>
</tr>
<tr>
<td>Sneddon syndrome</td>
<td>Livedo reticularis, generalised arterial occlusive disease that may affect the brain</td>
<td>S or A</td>
<td>Reese et al. (1993)</td>
</tr>
<tr>
<td>Divry–Van Bogaert syndrome</td>
<td>Livedo reticularis, noncalcifying leptomeningeal angiomatosis with progressive neurological impairment</td>
<td>S</td>
<td>Stone et al. (2001)</td>
</tr>
<tr>
<td>Macrocephaly–cutis marmorata telangiectatica or Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP)</td>
<td>Livedo reticularis, dysmorphism, CNS malformations, intellectual disability, macrocephaly syndrome</td>
<td>S or PIK3CA gene</td>
<td>Garavelli et al. (2005); Lapunzina et al. (2004); Mirzaa et al. (2012); Rivière et al. (2012)</td>
</tr>
<tr>
<td>PHACES syndrome</td>
<td>See text</td>
<td>S</td>
<td>Reese et al. (1993)</td>
</tr>
<tr>
<td>Familial cavernous malformation of CNS and retina (Gass syndrome)</td>
<td>Cavernous angiomas of the brain, multiple in 50% of cases, retinal angiomas, occasional cutaneous involvement</td>
<td>AD</td>
<td>Gass (1971); Dobyns et al. (1987); Backhouse and O’Neill (1998)</td>
</tr>
<tr>
<td>Wyburn–Mason syndrome (Dechaume–Blanc–Bonnet syndrome)</td>
<td>Retinal arteriovenous angioma, unilateral arteriovenous malformation extending from the retina along the visual pathways to the brainstem and sometimes the cerebellar hemisphere. Rupture of vessels frequent. Facial periorbital angioma</td>
<td>S</td>
<td>Gomez (1994); Lester et al. (2005)</td>
</tr>
<tr>
<td>Hereditary neurocutaneous angiomatosis</td>
<td>Cutaneous angiomas of skin, cerebral or cerebellar arteriovenous malformations</td>
<td>AD</td>
<td>Drigo et al. (1994); Leblanc et al. (1996)</td>
</tr>
<tr>
<td>Von Hippel–Lindau disease</td>
<td>See text (cutaneous involvement possible)</td>
<td>AD VHL gene</td>
<td>Joerger et al. (2005); Glasker (2005); Nordstrom-O’Brien et al. (2010)</td>
</tr>
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</table>

*Various genetic factors are being studied but most cases are sporadic.*

CNS, central nervous system; S, sporadic; AD, autosomal dominant.
The pathological features and course of ataxia-telangiectasia are more closely related to the heredodegenerative disorders, in particular the spinocerebellar degenerations of which this disease represents; however, the second most common type after Friedreich ataxia is discussed in this chapter because, from a purely clinical point of view, its presentation and diagnosis are mainly those of a neurocutaneous syndrome in a majority of patients, even though it can also be regarded as a degenerative genetic condition.

Ataxia-telangiectasia is a heredofamilial disease of DNA instability, characterised by progressive cerebellar ataxia and choreoathetosis, progressive oculocutaneous telangiectasias, immunodeficiency with susceptibility to sinopulmonary infections, impaired organ maturation, hypersensitivity to ionising radiations and a high incidence of malignancies. It is a multisystem genetic disorder with an autosomal recessive inheritance. The responsible gene ATM (AT mutated) on chromosome 11q22–23 (Savitsky et al. 1995; Shiloh 1995) codes for a protein (ATM protein) with similarities to mammalian phosphatidylinositol-3′-kinases. The ATM protein is a nuclear protein that plays a crucial role in the stability and repair of double-stranded DNA and thus in the control of the stability of the cell cycle and in the protection of the genome. Numerous mutations are known, most being null mutations (Gilad et al. 1996). Less severe mutations are encountered, giving rise to less severe clinical cases (Gilad et al. 1998; Taylor and Byrd 2005).

Mechanisms and Pathology of Ataxia-Telangiectasia

The abnormal double-stranded DNA maintenance has widespread consequences. The ATM protein, a protein kinase, is thought to be essential for control of the cell cycle, in particular at the checkpoints G1 and G2/M. It plays a major role in signalling defects of double-stranded DNA and in blocking cell cycle allowing repair of the genome (Lavin et al. 2005). Its failure thus allows induced activation of the cell cycle, which may be deviated toward apoptosis. One important consequence is the abnormal sensitivity of ataxia-telangiectasia cells to ionising radiation and certain radiomimetic chemicals but not to ultraviolet irradiation (Barlow et al. 1999). The cell cycle allowing repair of the genome increasing sensitivity to malignancies even in the heterozygous state. The mechanisms responsible for neurological disease, thymus aplasia, telangiectasias, growth retardation and impaired organ maturation have not been elucidated. There is a general disturbance in tissue differentiation that accounts for the frequent elevation of alpha-fetoprotein (AFP), a fetal serum protein of hepatic origin that indicates dedifferentiation of liver cells.

Considerable work suggests that ataxia-telangiectasia may be associated with dysregulation of the immunoglobulin gene superfamily, which includes genes for T-cell receptors (Peterson and Funkhouser 1989). The normal switch from the production of IgM to IgG, IgA and IgE is defective, and the same may apply to the switch from immature T-cells that express the gamma/delta rather than the alpha/beta receptors (Carbonari et al. 1990). Conceivably, absence or mutation of a single protein coded for by chromosome 11 could explain the immunological and perhaps even the neurological features of the disease (Kastan 1995).

The major neuropathological lesion in the CNS is degeneration of Purkinje and granule cells in the cerebellum (De Léon et al. 1976; Paula-Barbosa et al. 1983). Usually, no vascular abnormalities are found except late degenerative gliovascular nodules in the white matter. Lesions of the basal ganglia are found only occasionally (Boder 1985). Degeneration of spinal tracts and anterior horn cells is often present in late cases. Nucleocytomegaly is a feature of several cell types throughout the body, notably in peripheral nerves (De Léon et al. 1976).

Clinical Features of Ataxia-Telangiectasia

Neurological findings

The main neurological manifestations of ataxia-telangiectasia are cerebellar ataxia and abnormal eye movements, in the form of ocular motor apraxia, which is present in most cases, and choreoathetosis that occurs in 25% of patients (Boder 1985). The ataxia has its onset in infancy, becoming evident when the child begins to walk. From this early stage, ataxia is associated with abnormal head movements, and affected children have a peculiar gait like ‘little clowns’ that is highly suggestive. However, ocular motor apraxia often appears only after some years. The ataxia is relentlessly progressive but the pace is variable.
even in the same sibship. Dysarthria of cerebellar type is the rule; intention tremor and myoclonus may be observed. Various movement disorders are often present. Choreaathetosis may be so marked in some patients as to overshadow or mask the ataxia. A dystonic component is possible and may seldom be prominent. Orpharyngeal dystonia may lead to aspiration (Lefton-Greif et al. 2000), and the relatively immobile face with a peculiar slow-spreading smile, which is a suggestive symptom, may be due to extrapyramidal involvement. Late pyramidal signs may be present. Ocular motor signs are diagnostically important because they may precede the appearance of telangiectasias. Saccades are slowly initiated and hypometric, so that fixation of a target is obtained by head rather than eye deviation, often in association with a head thrust or forced blinking as in Cogan ocular motor apraxia (Baloh et al. 1978), but is present in both horizontal and vertical gaze. Eye deviation, when obtained, is saccadic and often halts midway; and optokinetic nystagmus is absent. Other ocular abnormalities include deficient accommodation, nystagmus, frequent blinking and photophobia (Riise et al. 2007). Peripheral system involvement is a late feature first manifested by absence or weakness of the tendon jerks. The peculiar appearance of children with ataxia-telangiectasia is often striking, with a characteristic gait and posture, a dull facies at rest, and abnormal head movements due to oculomotor defect. About 30% of patients have mild intellectual disability. A small head circumference (61%) and microcephaly (17%), both acquired after the second year of life, have been recognised as a major clinical feature (Nissenkorn et al. 2011).

Telangiectasias and Other Cutaneous Abnormalities

Telangiectasias are first noticed after 3 years of age, sometimes not until adolescence. They may be absent even later in some patients (Chung et al. 1994). Dilated conjunctival vessels, first noticed in the angles of both eyes, spread horizontally in the equatorial region of the conjunctive toward the corneal limb. They may involve the ears, eyelids, and cubital and popliteal fossae. In late childhood and adolescence, progeric skin changes may appear, as well as pigmentedary changes and café-au-lait spots. The skin often has an unusual appearance with evidence of premature ageing, café-au-lait spots (Ortonne et al. 1980), and warts or molluscum pendulum. Multiple skin cancers may develop especially in areas of previous X-irradiation.

Sensitivity to Infections

Patients with ataxia-telangiectasia are unusually sensitive to infections, mostly bacterial but to a lesser extent viral, in part as a result of immune globulin abnormalities (Nowak-Wegrzyn et al. 2004) and of deficiency of cellular immunity (Schubert et al. 2002) with decreased numbers of B-cell and of T4 and T8 lymphocytes. Nowak-Wegrzyn et al. (2004) found in 100 ataxia-telangiectasia patients that lymphopenia was present in 71%, and that immunoglobulin levels were lowered by 65% for IgG, 63% for IgA, 48% for Ig2, 23% for IgE, and only 18% for IgG. Approximately 10% of patients present with decreased serum IgG and IgA with normal or raised IgM levels. These patients are often erroneously diagnosed as hyper-IgM syndrome; thus, ataxia-telangiectasia should be considered in the differential diagnosis of patients with this syndrome (Noordzij et al. 2009; Pietrucha et al. 2010). Rare patients may have no immunodeficiency as a result of specific mutations (Toyoshima et al. 1998). The most common infections are those of the upper respiratory tract.

Repeated sinopulmonary infections were present in 48–81% of patients reviewed by Chung et al. (1994), but in the study of Nowak-Wegrzyn et al. (2004) only 15% of patients had pneumonia. Infections of viral origin in the latter series included warts, molluscum and herpes simplex, but none were severe. In a study by Chun and Gatti (2004), severe infection with progressive lung disease was present in one-third of children, one-third had sinopulmonary infection but not progressive lung disease, and the remaining third had only a normal incidence of infections. There was a good correlation between the occurrence of infections and immune-deficiency as assessed by laboratory tests. Such a correlation was not found in other series (Roifman and Gelfand 1985).

Overall, lung disease is thought to exhibit features of one or more of the following phenotypes: recurrent sinopulmonary infections with bronchiectasis, interstitial lung disease, and lung disease associated with neurological abnormalities (McGrath-Morrow et al. 2010).

Retardation of somatic growth is found in most patients, and many do not achieve normal puberty. In girls, this may be related to absence of ovary differentiation that is found in some patients.

Course and Prognosis of Ataxia-Telangiectasia

The neurological features of ataxia-telangiectasia are relentlessly progressive (Chun and Gatti 2004). In addition to the classic early features, older patients tend to develop other signs of spinocerebellar degeneration such as posterior cord involvement with loss of deep tendon reflexes and spinal muscular atrophy (Boder 1985; Kwast and Ignatowicz 1990; Hiel et al. 2006). Most patients are wheelchair dependent by 10–15 years of age, but mild forms are not rare and can be related to specific mutations of the ataxia-telangiectasia gene (Taylor and Byrd 2005). Early death is frequently due to pulmonary disease but malignancies are now the most common cause. The incidence is 60–300 times higher than in non-affected persons, and 49% of patients coming to autopsy had malignant tumours (Swift et al. 1991). The most common tumours are T-cell and B-cell lymphoreticular malignancies, especially non-Hodgkin lymphomas, lymphocytic leukaemia and Hodgkin lymphomas (Boder 1985), but other kinds of tumours also occur. Lymphoreticular neoplasms and leukaemia predominate in patients under 15 years of age, while epithelial tumours predominate in older patients. Malignancies are also thought to be more common in obligate heterozygotes for the mutant ataxia-telangiectasia gene than in the general population (Swift et al. 1991). The frequency of cancers, especially breast carcinomas, is reported to be three to six times greater than in the general population (Thompson et al. 2005), and this information has to be included in genetic counselling,
although it remains a disputed issue (Gumy-Pause et al. 2004; Tamimi et al. 2004). In older patients, insulin-resistant diabetes develops in half the patients but is not responsible for ketosis.

**Diagnosis and Laboratory Markers of Ataxia-Telangiectasia**

The clinical diagnosis of ataxia-telangiectasia is easy when both cardinal features are present. Before the appearance of telangiectasias, the diagnosis of ataxic cerebral palsy is often made. However, ocular motor abnormalities and the ‘little clown’ gait are suggestive of ataxia-telangiectasia.

Laboratory markers are important for both diagnosis and prognosis. The most constant markers are elevated levels of AFP and carcinoembryonic antigen, and chromosomal abnormalities, especially inversions and translocations involving chromosomes 7 and 14 (Hecht and Hecht 1985), which are regarded as pathognomonic for ataxia-telangiectasia. Neither of these abnormalities is always found, however, and their demonstration may require specific techniques available only in some centres.

The demonstration of humoral or cellular immunological defects may also suggest an early diagnosis, although such defects are nonspecific and less frequently present (Roifman and Gelfand 1985). The dysgammaglobulinaemia of ataxia-telangiectasia includes absence or low level of IgA including secretory IgA, normal or low level of IgG, and elevated or normal level of IgM. A deficit in Ig2 and Ig4 subclasses has been demonstrated in several patients, and IgE may also be absent or low (Oxelius et al. 1982; Schubert et al. 2002). Defects of cellular immunity include a low lymphocyte count, a poor response to skin tests for common antigens, low T-lymphocyte proliferation in the presence of mitogens, and deficient antibody production to viral or bacterial antigens. Excessive T-cell suppressor activity and intrinsic B-cell defects have been described in some patients, suggesting disturbances of immunoregulatory mechanisms.

Chromosomal abnormalities, especially the increased incidence of breaks on certain chromosomes, remain of considerable practical value. Survival of cell colonies after exposure of cell cultures to ionising radiation is of definitive diagnostic value (Chun and Gatti 2004) but not a routine procedure. These tests are being supplanted by molecular diagnosis, which is also considered for the prenatal diagnosis although this is difficult and not always possible. Most mutations of the ataxia-telangiectasia gene are truncating or splicing mutations; only about 10% are missense mutations. Other investigations are of less importance. CT and MRI often show evidence of nonspecific cerebellar atrophy. Nerve conduction velocities may be slowed, and denervation of anterior horn cell type may be found in older patients (Dunn 1973).

**Atypical and Variant Forms of Ataxia-Telangiectasia**

Patients with atypical forms of ataxia-telangiectasia have recently attracted interest. Some cases are undoubtedly part of the spectrum of the disease, with a slow course and prolonged survival and incomplete expression, e.g. absence of ocular motor signs (Trimis et al. 2004). Others include markedly abnormal features such as intellectual disability and spasticity (Meshram et al. 1986), peripheral neuropathy as a predominant sign (Térenty et al. 1978), and absence of telangiectasia persisting into adulthood (Byrne et al. 1984). Patients with variant ataxia-telangiectasia tend to present with movement disorders often mimicking forms of primary torsion dystonias (Verhagen et al. 2009; Saunders-Pullman et al. 2012; Charlesworth et al. 2013). Some of these patients lack one or the other of the laboratory markers. They confirm the genetic heterogeneity of the disease, which has been demonstrated by molecular studies (Taylor and Byrd 2005). It seems that there is a clear genotype–phenotype relation, since the severity of the phenotype depends on the amount of residual kinase activity as determined by the genotype. Thus, ataxia-telangiectasia should be considered in patients with an otherwise unexplained movement disorder. Early diagnosis is important given the increased risk of malignancies and the higher risk for side effects of subsequent cancer treatment (Verhagen et al. 2009).

The Nijmegen breakage syndrome (Seemanova et al. 1985) manifested by microcephaly, immunodeficiency, and growth retardation, tends to be considered as a variant of ataxia-telangiectasia (variant-1), with a similar tendency to develop lymphoreticular malignancies, probably because they share defects of the DNA repair systems. It is an autosomal recessive disorder caused by mutation in the NBS1 gene (Carney et al. 1998; Varon et al. 1998).

Other rare conditions that share some features with ataxia-telangiectasia include the dysequilibrium–diplegia syndrome (Hagberg et al. 1970; Graham-Pole et al. 1975) in which immunodeficiency is a major feature. This syndrome is associated with purine nucleotide phosphorylase deficiency (Soutar and Day 1991), caused by mutation in the PNP gene (Williams et al. 1987). Patients with this disorder have normal immunoglobulins and pyramidal tract signs, and in one case heterotopia and cortical dysplasia were present (Soutar and Day 1991). Other syndromes with neurological features, especially microcephaly, in association with chromosomal instability may have some relationship to ataxia-telangiectasia, especially the tendency to develop lymphoreticular malignancies.

**Management of Ataxia-Telangiectasia**

Although no specific treatment is available, several features of ataxia-telangiectasia are accessible to active therapy. This applies especially to infections, and the lifespan of patients with ataxia-telangiectasia has been clearly prolonged by antibiotic treatment. Prevention of infections by regular injection of immunoglobulins is considered useful. Fetal thymus implants and stimulants of the immunological system have given inconclusive results.

Treatment of neurological manifestations is disappointing. Propanolol and sulpiride may improve fine motor coordination in a few patients. Rehabilitation and adequate educative
support are always necessary. One adult patient had improvement in his gait ataxia with treatment with the GABAergic medications pregabalin and tiagabine (Gazulla et al. 2007). Some improvement in movement disorders has also been reported with the use of amantadine sulphate (Nissenkorn et al. 2013). In a multicentre, double-blind, randomised, placebo-controlled trial, oral betamethasone reduced ataxia as measured by standardised ataxia scales (Zannoli et al. 2012). However, the long-term safety and effectiveness of oral steroid therapy is still being evaluated.

The use of radiotherapy and chemotherapy in conventional doses is contraindicated in ataxia-telangiectasia patients. Reduced doses of X-rays or chemicals, avoiding bleomycin, actinomycin D and cyclophosphamide, have given favourable results in a few patients. Regular surveillance of patients for the emergence of cancers and leukaemia should be strict. This also applies to heterozygotes and should probably be part of the family management.

**DISORDERS RELATED TO ATAXIA-TELANGIECTASIA**

**ATAXIA-TELANGIECTASIA-LIKE DISEASE**

Some patients presenting with features that mimic ataxia-telangiectasia are not associated with mutations in the ataxia-telangiectasia gene. In such cases the disorder seems to be less severe. Increased sensitivity to ionising radiation is present, as are chromosome breakages (Taylor et al. 2004). However, malignancies have not been reported (Delia et al. 2004). The emergence of cancers and leukaemia should be strict. This also applies to heterozygotes and should probably be part of the family management.

**ATAXIA–OCULOMOTOR APRAXIA**

Although ataxia-oculomotor apraxia (AOA) does not feature cutaneous abnormalities, it is mentioned in this chapter because of its striking resemblance to ataxia-telangiectasia. Four distinct entities are recognised: AOA1, AOA2, AOA3, and AOA4 (see also Chapter 22).

AOA1 appears to occur predominantly in children, in contrast with AOA2, which is more frequent in adults (Le Ber et al. 2004). It is an autosomal recessive ataxia associated with oculomotor apraxia, hypoalbuminaemia and hypercholesterolaemia, with onset in childhood and even in infancy (Ito et al. 2005). Chorea and peripheral neuropathy are frequent manifestations. AFP levels are normal (Aicardi et al. 1988; Gasco et al. 1995; Le Ber et al. 2003). The responsible gene, APTX on chromosome 9q13, encodes the protein aprataxin. It is probably important in single-strand DNA break repair. No telangiectasias are seen; there is no increased frequency of malignancies and no chromosome breakages are noted. The course is slowly progressive and may become static. MRI demonstrates marked cerebellar atrophy (Barbot et al. 2001; Shimazaki et al. 2002; Le Ber et al. 2003). The phenotype is variable, some patients having no oculomotor apraxia or presenting with a neuropathy.

In AOA2, the clinical features are similar, with a later onset in early adolescent years. AFP is moderately elevated in three-quarters of the patients (Le Ber et al. 2004). Oculomotor apraxia is constant (Le Ber et al. 2004; Duquette et al. 2005). The responsible gene SETHX on chromosome 9q34 codes for the protein senataxin whose role is not known. Anheim et al. (2009) retrospectively analysed 90 patients from 15 families with a genetically confirmed diagnosis of AOA2. The median age at onset was 14 years. Clinical features included polyneuropathy (97.5% of patients), cerebellar atrophy (96%), occasional oculomotor apraxia (51%), pyramidal signs (20.5%), head tremor (14%), dystonia (13.5%), strabismus (12.3%) and chorea (9.5%).

AOA3 is caused by a mutation in the PKR5 gene on chromosome 17p (Al Tassan et al. 2012); and AOA4 is caused by mutation in the PNKP gene on chromosome 19q13. Bras et al. (2015) reported 11 patients with age at onset from 1 to 9 years. Most patients presented with prominent dystonia and additional features included ataxia, oculomotor apraxia and peripheral neuropathy. Most patients became wheelchair-bound in the second or third decade. All patients had cerebellar atrophy and some of them increased alpha-fetoprotein and cholesterol.

**NEUROCUTANEOUS SYNDROMES WITH ABNORMAL PIGMENTATION**

**INCONTINENTIA PIGMENTI (BLOCH–SULZBERGER TYPE)**

Bloch–Sulzberger syndrome is a rare genetic disorder, observed almost exclusively in girls, probably transmitted as an X-linked dominant trait prenatally lethal in the majority of affected males. The responsible gene, IKBKG (inhibitor of kappa B kinase gamma, previously NEMO), is a modulator of the activation of the nuclear factor kappaB (NF-kappaB) signalling pathway (Fusco et al. 2004; Su et al. 2004) and maps to Xq28. When activated, NF-kappaB controls the expression of multiple genes, including cytokines and chemokines, and protects cells against apoptosis (Berlin 2002).

**Skin Features**

The skin lesions are striking. They consist of four distinct but somewhat overlapping stages (Rosman 1992; Mangano and Barbagallo 1993; Berlin 2002): vesicular, verrucous, pigmented...
and atrophic scarring. In the first stage, erythematous, papular, vesicular or bullous lesions are present at birth or during the first 2 weeks of life on the trunk and limbs. They are linear in distribution and last from days to months. Most resolve by 4 months of age. In the second stage, between the second and the sixth weeks, the lesions are variably pustular, verrucous or keratotic (O’Brien and Feingold 1985). Most lesions resolve by 6 months of age, but they may recur throughout childhood often during viral or bacterial infections or after routine vaccination (Patrizi 2004; Alikhan et al. 2010). They may disappear without sequelae or are followed by the development of pigmentation, characteristic of the third stage of the disease. Stage 3 occurs in 98% of patients. These pigmented grey-brown lesions are the hallmark of the disease and may be located outside the area of earlier lesions, and in 10% of patients are not preceded by them. The pigmentation persists into adulthood but tends to fade with the passing of time. Some patients can have pale areas of earlier lesions, and in 10% of patients are not preceded

Evidence of CNS infection. These are the most frequent neurological manifestations and appear to be the result of an arte-ritis that may be extensive and can be detected by angiography (Fiorillo et al. 2003; Hennel et al. 2003). Siemes et al. (1978), Shuper et al. (1990) and Hennel et al. (2003) found inflammatory lesions in all participants. Other pathological lesions are possible. Patients have been reported with reversible CNS white matter lesions (Bryant and Rutledge 2007; Lou et al. 2008) One patient had involvement of the anterior horn cells of the spinal cord (Larsen et al. 1987); in another case a migrational disorder was found (O’Doherty and Norman 1968).

Other Symptoms, Evolution and Management

Various eye lesions are present in one-third of patients, the most characteristic of which is a retrolental mass with detachment of a dysplastic retina (Rosenfeld and Smith 1983). This should be looked for systematically in affected infants, as early detection and therapy of the retinitis may protect vision (Wong et al. 2004).

Dental abnormalities (peg-shaped teeth) occur in 70% of patients. Treatment is symptomatic and includes ophthalmological interventions, antiepileptic agents, physiotherapy and corticosteroids. Orthopaedic measures as well as educational support are vital. Genetic counselling is an important part of management. The outcome is not necessarily bad and a normal long-term outcome may be observed in some patients (Steﬀan et al. 2004). Prenatal molecular diagnosis has been made (Steﬀan et al. 2004).

Bloch–Sulzberger syndrome is probably different from the Naegeli type of incontinentia pigmenti rather than a subtype of the same disease (Rosman 1992). The latter occurs in boys and girls.

**INCONTINENTIA PIGMENTI ACHROMIANS (HYPMELANOSIS OF ITO)**

Another condition that should be distinguished from Bloch–Sulzberger disease is hypomelanosis of Ito or incontinentia

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### Table 4.4 Incontinentia pigmenti diagnostic criteria

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria (supportive evidence)</th>
<th>Conditions for establishing incontinentia pigmenti diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical IP skin stages distributed along Blaschko’s lines: vesiculo-bullous stage; verrucous stage; hyperpigmented stage; and atrophic/hypopigmented stage.</td>
<td>Dental anomalies</td>
<td>No evidence of IP in a first-degree female relative:</td>
</tr>
<tr>
<td></td>
<td>Ocular anomalies</td>
<td>If lacking genetic IKBKG mutation data, at least two or more major criteria or one major and one or more minor criteria are necessary to make a diagnosis of sporadic IP</td>
</tr>
<tr>
<td></td>
<td>CNS anomalies</td>
<td>In the case of confirmed IKBKG mutation typical for IP, any single major or minor criterion is satisfactory for IP diagnosis.</td>
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<tr>
<td></td>
<td>Alopecia</td>
<td>Evidence of IP in a first-degree female relative:</td>
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<td></td>
<td>Abnormal hair (sparse hair, woolly hair, anomalies of eyebrows and eyelashes)</td>
<td>Any single major or at least two minor criteria.</td>
</tr>
<tr>
<td></td>
<td>Abnormal nails</td>
<td>In all cases eosinophilia and skewed X-chromosome inactivation supports diagnosis.</td>
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<tr>
<td></td>
<td>Palate anomalies</td>
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<tr>
<td></td>
<td>Nipple and breast anomalies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple male miscarriages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typical skin pathohistological findings</td>
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</table>

*Updated by Minić et al. (2014).*

IP, incontinentia pigmenti; CNS, central nervous system; IKBKG, inhibitor of nuclear factor kappa B kinase subunit gamma.
pigmenti achromians. This disorder is characterised by hypopigmented areas with a peculiar streaked or whorled appearance, often unilateral or with a strong unilateral predominance along the Blaschko lines (Pascual-Castroviejo et al. 1988; Gordon 1994) (Fig. 4.12). The appearance is variable with the possibility of pigmented rather than achromatic lesions and more commonly of an association of both. Associated abnormalities are described in 33–94% of patients. CNS involvement is most common, thus justifying the term neurocutaneous syndrome (Steiner et al. 1996; Ruggieri and Pavone 2000). Only about one in four have average or above average IQ, and more than 50% have some degree of learning disability (IQ <70). Seizures are common (about half the group), they can be of several types and infantile spasms occur in about one in 10 individuals with typical skin changes. Patients with hypomelanosis of Ito may present heterogeneous epilepsy phenotypes. At one extreme, there are patients with generalised seizures well controlled by antiepileptic drugs, whereas at the opposite extreme there are patients with severe, pharmacoresistant, focal seizures (Assogba et al. 2010). There is also a wide spectrum of EEG abnormalities from normal records to multifocal paroxystic features. Fast rhythm may be associated with areas of pachygyria (Ogino et al. 1994). Ito disease is one of the causes of hemimegalencephaly (Pascual-Castroviejo et al. 1988; Auriemma et al. 2000). Macrocephalus is present in about one in seven patients. Glover et al. (1989) found psychomotor delay in 14 of their 19 patients, nine had seizures, and two had severe sensorineural deafness.

Many cases of hypomelanosis of Ito are associated with psychiatric disorder including symptoms compatible with the diagnoses of psychosis, autism, atypical autism and Asperger syndrome have been described (Åkefeldt and Gillberg 1991; Zappella 1993; Davalos et al. 2001; Pascual-Castroviejo et al. 1998, 2006). Autism spectrum manifestations are known to occur (Åkefeldt and Gillberg 1991) in up to 10% of patients (Pascual-Castroviejo et al. 1988). Eye abnormalities (Rosenfeld and Smith 1983) include microphthalmia and related structural abnormalities, and were present in three of the 19 patients of Glover et al. (1989). Hemihypertrophy and scoliosis are commonly present. Imaging may show bilateral or unilateral hemispheric atrophy or areas of low attenuation in white matter or cerebellar atrophy (Pini and Faulkner 1995). MRI has shown the presence of neuronal heterotopia (Glover et al. 1989; Malherbe et al. 1993), and Steiner et al. (1996) reported a wide spectrum of major and minor imaging abnormalities. White matter signal abnormalities may be present, which is in agreement with the pathological findings of Fujino et al. (1995).

Most confirmed cases of hypomelanosis of Ito are sporadic, although dominant transmission has been suggested but not demonstrated. Girls seem to be more commonly affected than boys. Mosaicism for miscellaneous chromosome aberrations appears to be a common but not a constant cause of the disease (Taibjee et al. 2004; Lombillo and Sybert 2005).

Chromosome analysis should ideally be performed on keratinocyte cultures whereas lymphocyte and fibroblast cultures are usually negative. Prenatal diagnosis has been made (Steinberg Warren et al. 2001).

There is no treatment for the skin disorder, but cover-up make-up can be used if desired. Neurological, hearing and visual problems should be treated as indicated for those particular problems.

**NEUROCUTANEOUS MELANOSIS**

This rare disorder is characterised by cutaneous pigmented nevi and variable involvement of the meninges and CNS (Makkar and Frieden 2004) (Fig. 4.13). The nevi are of the giant type, often in ‘bath suit topography’ that covers the lower part of the trunk, the pelvis and the upper part of the lower limbs in two-thirds of patients and multiple small lesions in one-third. However, we have seen a child with biopsy-proven meningeal melanosis who had a single nevus of 5×5cm on one arm, and a lesion of similar size was encountered by de Andrade et al. (2004). The nevi are heavily pigmented and hairy. Kinsler et al. (2008) performed a retrospective study of 120 patients. MRI abnormalities were found in 18% of patients and were significantly associated with projected adult size of the largest congenital melanocytic nevus, particularly those greater than 40cm.

More than half the patients with congenital hairy nevi develop early CNS involvement, in the form of progressive hydrocephalus, probably as a result of proliferation of meningeal melanocytes with consequent blockage of CSF reabsorption or circulation or of meningeal or CNS malignant tumours (Di Rocco et al. 2004; Ramaswamy et al. 2012). There is often cystic dilatation of the cisterna magna (Barkovich et al. 1994). Other CNS findings include parenchymal neuromelanosis, and rarely choroid plexus papilloma, astrocytoma and posterior fossa arachnoid cyst (Kinsler et al. 2008). Seizures are common, and variable neurological deficits may result from parenchymal tumoural proliferation of melanocytes.
(Rhodes et al. 1991), such as hemiparesis, reduced muscle tone, spasticity, ataxia and global developmental delay (Kinsler et al. 2008).

The prognosis is poor in symptomatic patients, but hydrocephalus should be treated with a shunt (Di Rocco et al. 2004). An occasional patient survives many years but malignant degeneration of CNS lesions is extremely common.

Kinsler et al. (2013) suggested that single postzygotic NRAS mutations are responsible for multiple congenital melanocytic nevi and associated neurological lesions in the majority of patients.

OTHER NEUROCUTANEOUS SYNDROMES WITH ABNORMAL PIGMENTATION

Albinism refers to a group of inherited disorders in which there is a reduction or absence of melanin formation. Many types of albinism are known, and the main features of the condition are cutaneous and ocular rather than neurological. One remarkable finding is misrouting of the optic fibres, with an abnormally high proportion of crossed fibres and projection of only the most peripheral part of the temporal retina to the ipsilateral hemisphere, which may be demonstrated by study of the visual evoked potentials (Collewijn et al. 1985) and by appropriate MRI techniques (Hedera et al. 1994). Using MRI, Schmitz et al. (2003) found that the size and configuration of the optic chiasm in humans with albinism are distinctly different from the chiasms of normal control participants. Albino children also have a special pattern of cognitive function with a much higher score on verbal than on performance items (Cole et al. 1987).

Several rare syndromes of deficient pigmentation variably feature immunodeficiency (macrophagic activation syndrome) and/or neurological signs. Chediak–Higashi syndrome (CHS) associates a peripheral neuropathy with immune and haematological abnormalities. Chediak–Higashi syndrome is caused by homozygous or compound heterozygous mutation in the lysosomal trafficking regulator gene \( LYST \) (Barbosa et al. 1997). Severe neurological problems affecting the CNS with seizures, intellectual disability and motor deficits are prominent features in Hermansky–Pudlak (\( HPS1 \) gene), Griscelli (type 2, \( RAB27A \) gene) and Elejalde (or Griscelli type 1, \( MYO5A \) gene) syndromes (Oh et al. 1996; Pastural et al. 1997; Ménasché et al. 2000; Scheinfeld 2003). Griscelli type 2 or partial albinism with immunodeficiency syndrome is characterised by relapsing neurological symptoms, by the presence of demyelination beginning and predominating in the posterior fossa (Brismar and Harfi 1992) and spreading to involve the whole white matter, and the absence of characteristic granulations, and differs from Chediak syndrome by different hair and skin microscopic findings (Mancini et al. 1998).

Some other syndromes in this category are listed in Table 4.5.
### Table 4.5 Some rare neurocutaneous syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main features</th>
<th>Genetics</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Syndromes with hamartomatous tendency</strong></td>
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</tr>
<tr>
<td>Encephalo-cranio-cutaneous lipomatosis and Dellemann syndrome(^a)</td>
<td>Microgyria, brainstem abnormalities, unilateral scalp lipomas, porencephaly</td>
<td>S</td>
<td>Moog et al. (2007); Moog (2009); Pascual-Castroviejo et al. (2005b)</td>
</tr>
<tr>
<td>Proteus syndrome</td>
<td>See text</td>
<td>S</td>
<td>Thiffault et al. (2004); Turner et al. (2004)</td>
</tr>
<tr>
<td>Bannayan–Riley–Ruvalcaba syndrome</td>
<td>See text</td>
<td>AD(^b)</td>
<td>Hendricks et al. (2003)</td>
</tr>
<tr>
<td>Endocrine neoplasia type b2</td>
<td>Subcutaneous neurofibomas of lips, tongue and digestive tract, thickened inverted eyelids, medullary thyroid cancer, pheochromocytoma, marfanoid habitus, pes cavus, scoliosis, cutaneous neurofibromas</td>
<td>AD(^c) or S</td>
<td>Griffiths et al. (1990)</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>See text</td>
<td>AD(^d) or S</td>
<td>Hanssen and Fryns (1995); Perez-Nunez et al. (2004)</td>
</tr>
<tr>
<td><strong>Syndromes with abnormal pigmentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentiginosis–deafness–cardiopathy/LEOPARD syndrome</td>
<td>Lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary artery stenosis, abnormal genitalia, retardation of growth, deafness, intellectual disability</td>
<td>AD</td>
<td>Schievink et al. (1995); Sarkozy et al. (2004); Ogata and Yoshida (2005); Limongelli et al. (2008)</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>White hairlock, heterochromia iridum, dystopia canthorum, deafness; variable frequency with subtype of syndrome</td>
<td>AD</td>
<td>Pardono et al. (2003); Pingault et al. 2010</td>
</tr>
<tr>
<td>Chediak–Higashi syndrome</td>
<td>Partial albinism, recurrent infections, neurological deficits, lymphoproliferative syndrome</td>
<td>AR</td>
<td>Van Hale (1988)</td>
</tr>
<tr>
<td>Familial spastic diplegia with crural hypopigmentation</td>
<td>Paraplegia, slow nerve conduction velocities</td>
<td>AR(^e) 1q24-q32</td>
<td>Stewart et al. (1981); Blumen et al. (2003)</td>
</tr>
<tr>
<td>Sunohara syndrome</td>
<td>Anosmia, hypogonadism, neurological defects</td>
<td>XR</td>
<td>Sunohara et al. (1986); Cuevas-Covarrubias, et al. (2008)</td>
</tr>
<tr>
<td>Ichthyosis with neutral lipid storage</td>
<td>Ataxia, sensorineural deafness</td>
<td>AR</td>
<td>Williams et al. (1985)</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutis verticis gyrata</td>
<td>Furrowed scalp, associated seizures and/or intellectual disability</td>
<td>S(^g)</td>
<td>Striano et al. (1996); Samira et al. (2014)</td>
</tr>
</tbody>
</table>

\(^a\) Encephalocraniocutaneous lipomatosis and Dellemann syndrome may belong to the same entity.

\(^b\) Sporadic cases are frequent. A mutation of the *PTEN* gene is frequent.

\(^c\) The dominant form is associated with mutations in the proto-oncogene RET.

\(^d\) Cowden syndrome is often associated with mutations in the *PTEN* gene.

\(^e\) S, sporadic; AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.
Chapter 4  Neurocutaneous Diseases and Syndromes

**NEUROICHTHYOSIS SYNDROMES**

The term neuroichthyosis refers to the syndromes that associate ichthyosis or ichthyosiform dermatoses to central or peripheral nervous system involvement.

**SJÖGREN–LARSSON SYNDROME**

Sjögren–Larsson syndrome combines intellectual disability and spastic diplegia with congenital ichthyosis (Rizzo et al. 1989). Patients are born preterm in 70% of cases. Spasticity becomes apparent between 4 and 30 months of age, is most pronounced in the legs and fairly slight in the arms. All patients have cognitive impairment, which varies from slight to severe, almost all have a mild-to-moderate dysarthria and one-third of them present epilepsy (Jagell et al. 1981; Gånemo et al. 2009; Fujikschot et al. 2012). Atypical retinitis pigmentosa with macular glistening dots is an almost constant feature but may easily escape detection (Jagell and Heijbel 1982; Willemsen et al. 2001). Peripheral involvement may occur. MRI may demonstrate a leukoencephalopathy with delayed myelin deposition, mild persistent white matter deficit (Hussain et al. 1995) and periventricular gliosis. Magnetic resonance spectroscopy shows accumulation of lipids in the white matter and a normal grey matter (Willemsen et al. 2004). The disorder is transmitted as an autosomal recessive trait. Several mutations in the gene \( ALDH3A2 \) encoding the fatty acid dehydrogenase FALDH are known (Rizzo et al. 1999; Carney et al. 2004). A defect of fatty alcohol metabolism is present, with deficiency of nicotinamide–adenine dinucleotide oxidoreductase in skin and leukocytes (De Laurenzi et al. 1996; Rizzo 2014). Prenatal diagnosis is possible (Rizzo et al. 1994). Dietary treatment is not successful (Maaswinkel-Mooij et al. 1994). Gene therapy is being tried (Haud and Braun-Falco 2006). The diagnosis depends on measurements of fatty aldehyde dehydrogenase or of the oxidoreductase complex in fibroblasts from skin biopsies, but now can be confirmed by genetic analysis. Identification of abnormal urinary excretion of leukotriene B4 and its metabolites can also be useful (Gordon 2007). Somewhat similar syndromes have been observed, one without metabolic deficit (Scalais et al. 1992) and one with prominent myoclonus (Amano et al. 1995).

**TRICHOTHIODYSTROPHY**

Trichothiodystrophy (TTD) is also known as Tay disease or Pollitt syndrome and it has also been described by several other acronyms: PIBIDS (photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility and short stature), IBIDS and BIDS (Baden et al. 1976). It is one of several related syndromes associated with abnormalities of DNA repair.

TTD is inherited as an autosomal recessive trait and results from mutations in one of several different DNA repair genes (XPA, XPD or TTDA) (Stefanini et al. 1986; Weeda et al. 1997; Giglia-Mari et al. 2004; Morice-Picard et al. 2009) and \( TTDNI \), a gene of unknown function (Nakabayashi et al. 2005). Although XPA and XPD mutations are also seen in xeroderma pigmentosum, a disease with a 1000-fold increase in skin cancer, patients with TTD have not been reported to have an increase in cancer.

Affected children have brittle and sparse hair, eyebrows and eyelashes. Microscopically, the hair shows ‘tiger banding’ and shaft abnormalities on polarised light examination (Liang et al. 2005), and the sulphur content is reduced to about half the usual value, as is the cystine content. Faghri et al. (2008) reviewed 112 published cases and reported that the majority of patients’ present intellectual impairment (86%), short stature, ichthyosis (65%) and ocular abnormalities such as cataracts. Many of them have abnormal characteristics at birth (55%) and maternal pregnancy complications. Recurrent infections in 46% are related with a high mortality rate at a young age, and photosensitivity is present in 42%.

Cerebellar and cerebral atrophy (Yoon et al. 2005), microcephaly, ataxia and calcification of the basal ganglia have been reported.

**OTHER NEUROICHTHYOSIS SYNDROMES**

Some other neuroichthyosis syndromes are listed in Table 4.5.

**MISCELLANEOUS NEUROCUTANEOUS SYNDROMES**

**NEVOID BASAL CELL CARCINOMA (GORLIN-GOLTZ SYNDROME)**

This is the most important among the rarer neurocutaneous syndromes. It is a complex disease with skin, bone and CNS manifestations, and a tendency to the development of neoplastic lesions, including medulloblastoma (Evans et al. 1993; Shanley et al. 1994; Amlashi et al. 2003).

Basal cell carcinomas are a constant feature of the syndrome but develop before puberty in only 15% of patients and are mainly located on the face, neck and upper trunk. Palmar and plantar cutaneous pits are a frequent feature.
Cysts of the jaw usually develop before 10 years of age. An early diagnosis in infants is possible by taking into account family antecedents and uncharacteristic features such as bone anomalies and malformations (Pastorino et al. 2005). CNS abnormalities include, in addition to posterior fossa tumours, calcification of the falx cerebri and, less frequently, of the tentorium cerebelli and the petroclinoid ligament; agenesis of the corpus callosum, bridging of the sella turcica; and occasionally intellectual disability (Titinchi et al. 2013; Larsen et al. 2014).

Klein et al. (2005) found mutations of the PTC1 gene on chromosome 9q31 in 44 of 106 patients. In affected members of a Chinese Han family, Fan et al. (2008) identified a heterozygous germline mutation in the PTCH2 gene. In a family exhibiting atypical signs and symptoms, Pastorino et al. (2009), analysed the PTC1 gene but found no mutations. Analysis of the SUFU gene, which like PTC1 and PTCH2 is a component of the same signalling pathway, revealed a splice site mutation in the proband and his father. The basic defect is unknown but there is an increased sensitivity of the skin to X-irradiation. Basal cell carcinomas have developed in the scalp and paraspinal area exposed to the radiation portal after treatment of medulloblastoma in some cases.

Patients with this syndrome should be carefully watched for the possible development of an aggressive cancer. Small odontogenic cysts and skin tumours that show ulceration or haemorrhage should be removed. Successful treatment for the basal cell carcinomas with topical imiquinone and wide-area-5-aminolevulinic acid photodynamic therapy (Oseroff et al. 2005) has been reported.

**PROGRESSIVE HEMIFACIAL ATROPHY (PARRY–ROMBERG DISEASE)**

This rare condition is characterised by progressive hemifacial atrophy. The most common early sign is a painless cleft, the coup de sabre, near the midline of the face which marks the boundary between the normal and atrophic tissues. Characteristically, the atrophy starts in the first decade of life and progresses slowly for several years.

This cutaneous syndrome may be associated with neurological manifestations (Chung et al. 1995). Seizures, often focal in type and more often arising from the hemisphere ipsilateral to the side of the facial atrophy, are the most frequent symptom. Unilateral or bilateral motor deficit, impaired sensory function, optic atrophy and involvement of cranial nerves may occur. Intracranial calcification is seen in some patients, and hemispheric atrophy has been demonstrated (Terstegge et al. 1994; Doolittle et al. 2015). Vascular abnormalities are present in some cases (Strenge et al. 1996; Taylor et al. 1997). The neurological disease may be progressive and even dementia has been reported. Cortical dysplasia was shown by MRI in four patients (Dupont et al. 1997). The skin and facial atrophy is also progressive over several years but eventually stabilises.

The relationship between en coup de sabre morphea and Parry–Romberg syndrome is still unclear. They frequently coexist and are likely both variants of morphea (Tollefsen et al. 2007).

**LIPOID PROTEINOSIS (URBACH–WIETHE DISEASE)**

Lipoid proteinosis is caused by mutation in the gene for the extracellular matrix protein 1, ECM1 (Hamada et al. 2002). It is also known as cutaneous mucous hyalinosis, and is characterised by a peculiar infiltration of the skin and mucous membranes by a hyaline substance resulting in thick skin with yellowish papules, a typical disposition on the margin of the eyelids and infiltration of the tongue and lips. Hoarseness and dysphonia (Van Hougenhouk-Tulleken et al. 2004) linked to an infiltration of the larynx is the most common manifestation at onset and it may be the only sign in early infancy. Imaging of the head may show calcification of the amygdalar region bilaterally (Özbek et al. 1994; Appenzeller et al. 2006). Thus, neurological involvement may occur in the form of focal seizures. A specific disturbance of emotion perception and recall (Siebert et al. 2003) may also be related to this frequent amygdalar involvement. Recently acitretin was used in the treatment of lipoid proteinosis with some effect in cutaneous lesions and hoarseness (Dertlıoğlu et al. 2014).

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Chapter 4 Neurocutaneous Diseases and Syndromes


Genetic Anomalies and Dysmorphic Syndromes

Karine Pelc and Bernard Dan

- Down Syndrome
- Fragile X Syndrome
- Rett Syndrome
- Angelman Syndrome
- Prader–Willi Syndrome
- The 22q11.2 Deletion Syndrome
- Williams Syndrome
- Cornelia De Lange Syndrome
- Noonan Syndrome
- Turner Syndrome
- Klinefelter Syndrome
- Smith–Magenis Syndrome
- Sotos Syndrome
- Cri-Du-Chat Syndrome
- Kabuki Syndrome
Genetic Anomalies and Dysmorphic Syndromes

Karine Pelc and Bernard Dan

The process of medical diagnosis aims to link observable signs to putative factors that underlie or at least facilitate the occurrence of these signs. The notion of phenotype refers to the characterisation of observable properties relating to clinical knowledge. In most chapters in this book, as in much of current clinical practice, this search often targets genetic determinants. The common use of the term ‘phenotype’ thus links it with the notion of genotype, i.e. the genetic basis that is expressed as the phenotype. However, the general concept is much wider than the implied focus on the genotype–phenotype relationship. In any case, careful observation of a patient’s phenotype is the only way to make a clinical diagnosis.

Many genetic syndromes have both physical and behavioural manifestations with distinctive social, cognitive and motor profiles. The course is not static with age, and presentation typically varies according to the level of learning disability and a host of environmental, developmental and therapeutic influences.

The phenotypic approach is a royal road to pathophysiological reasoning, which incorporates the molecular dimension of the genotype where applicable. Observed features can be tentatively explained by known physiology and gene function. For example, the propensity for more severe neurological impairment in patients with Angelman syndrome, associated with 15q11-q13 microdeletion, compared with other molecular causes has been hypothesised to be the result of hemizygosity of GABA$_A$-receptor subunits impairing $\gamma$-aminobutyric acid (GABA)-related neural synchrony (Dan 2009). The phenotypic approach is also important for management planning, because some phenotypic features may constitute targets, constraints or facilitating opportunities, (e.g. self-injury in Lesch–Nyhan syndrome (see Chapter 9)), impaired manipulative function in Rett syndrome or attention seeking behaviour in Angelman syndrome in Smith–Magenis syndrome.

A medical diagnosis is often expressed as a syndrome, i.e. an association of symptoms and signs that reflect physiological dysfunction, which may themselves be the result of different causes. When such an association has previously been typified, the search for the cause of the problems is much easier. When a syndrome has not been recognised previously, the identification of relevant symptoms and signs from the many aspects of the patient’s presentation is much more difficult, and requires an exquisite combination of medical knowledge, intuition and judgement.

Many syndromes have a genetic background, whether a single gene defect (e.g. Apert syndrome; see Chapters 6, 22, 23), chromosomal abnormalities (e.g. Down syndrome), microdeletion (e.g. Prader–Willi syndrome) or polygenic disorders (e.g. the autism spectrum disorder [ASD]; see Chapter 29).

When faced with the description of a syndrome, clinicians have to pay particular attention to dysmorphic features, i.e. congenital defects and abnormalities of body structure that relate to morphogenesis impairment in particular tissues. Some of them are pathognomonic and may lead to the early detection and intervention, for example, pulmonary artery stenosis in Williams syndrome (Ahmad and Vettukattil 2010). Although different processes underlying dysmorphic features may be disrupted by external agents, morphogenesis is highly determined by the interplay of many genetic determinants, which vary widely within the population. Malformations result from a basic alteration of structure, which typically occurs before 10 weeks’ gestation, (e.g. cleft palate, anencephaly, limb agenesis). They may also occur later in pregnancy as exemplified in brain cortex dysplasias (see Chapter 3). Malformations can occur in ‘sequences’ of multiple defects resulting from a single primary malformation, (e.g. talipes) and hydrocephalus can result from a lumbar neural tube defect (see Chapter 1). Malformation sequences differ from ‘associations’, which are groups of anomalies that occur more frequently than would be expected by chance alone, but do not have a unified aetiology, (e.g. VATER-vertebral anomalies, anal atresia, cardiac defects, tracheo-oesophageal fistula and/or oesophageal atresia, renal and radial anomalies and limb defects) association.

In clinical practice it is often difficult to determine whether the observed features indicate a syndrome or represent variations that occur in the general population. Comparison with other family members is useful, as are anthropometric measurements to identify abnormalities quantitatively with reference to growth charts of different parts of the body (including the face), obtained for the appropriate sex and ethnic background. The following elements raise suspicion of a genetic aetiology: congenital anomalies, unusual aspect,
growth deficit (e.g. short stature or failure to thrive), developmental delay or regression, cognitive impairment, failure to develop secondary sexual characters or ambiguous genitalia.

History taking should concentrate on setting up a detailed pedigree to evaluate an eventual family history and mode of inheritance. A detailed history of the pregnancy is important, for example, oligohydramnios may imply an aberrant force that caused malformation mechanically, and abnormal fetal position or decreased fetal movements suggest abnormal fetal tone. Environmental hazards for the fetus may help to exclude genetic disorders as a cause, for example, maternal conditions such as diabetes mellitus, hypertension, thyroid problems, phenylketonuria (see Chapter 9) or myasthenia gravis (see Chapters 22, 26), infections, use of drugs and other exposures. A large placenta, which may be a feature of Beckwith–Wiedemann syndrome, could be a valuable hint. The neonatal history, including birth measurements, is also important. A history of growth and neurological development should be investigated carefully, the association of failure to thrive or early onset obesity with milestone delay may be clues to genetic disorders, (e.g. a glycosylation defect (see Chapter 9) or Prader–Willi syndrome, respectively).

Physical examination may record unusual head shape, (e.g. trigonocephaly or brachycephaly), or abnormal head circumference, i.e. microcephaly or macrocephaly. Synophrys (i.e. fused eyebrows), is a feature of Cornelia de Lange syndrome. The inner canthal distance, palpebral fissures (slanting and length), the eyes themselves, the shape, rotation and position of the ears, and nose and mouth morphology can all provide relevant signs, and so can examination of the hands and feet (e.g. brachydactyly or short fingers or toes, arachno-, clino-, poly- or syndactyly), skin (pigmentation, scales, appendages) and hair (amount, texture, hairline), and joints (shape, mobility). The abdomen should be examined carefully for wall defects (omphalocele, gastrochisis), hepatosplenomegaly and abnormal genitalia.

Behavioural features should also be observed with respect to evocative behavioural phenotypes, i.e. distinctive associations of abnormalities in domains such as cognition, language, social skills and motor control, which are known to be associated with specific biological disorders (e.g. Williams, Lesch–Nyhan (see Chapter 19), fragile X, Angelman and Rett syndromes, among others).

Radiological examination highlights bony changes and neuroimaging highlights brain structures.

Finally, laboratory tests, including genetic testing, which until recently were essentially used to confirm and refine the clinical diagnosis, now play a prominent role in agnostic exploration, which has increasingly supplanted directed exploration of suspected conditions. Laboratory tests can also contribute to unravelling the cause of an as yet unclassified syndrome. This journey from phenotype to genotype takes the clinician through the complexities and singularities of individual patients. Apart from targeted genetic testing, which is still favoured when the clinical presentation strongly evokes a well-defined neurogenic condition with minimal or no genetic heterogeneity, technological advances have dramatically increased the diagnostic yield in the last few years. Comparative genomic hybridisation (CGH) array has replaced conventional karyotyping as a routine first-line investigation in children with intellectual disability that is or is not associated with a dysmorphic syndrome in many settings. It allows for detection of small chromosomal deletions and duplications (called copy number variants), with a higher resolution than conventional karyotyping (down to few dozen kilobases), leading to a significant increase in aetiological diagnoses through the detection of chromosomal deletions and duplications, including many newly recognised syndromes. Whole-exome sequencing, which allows for the detection of nucleotide substitutions and small insertions or deletions, is complementary to CGH array in the genetic work-up. Its use in a clinical work-up has drastically increased the diagnostic yield, in both the conditions described in this chapter and a wide range of neurological disorders with Mendelian inheritance. These advances have proved to be extremely useful for patients, families and clinicians, but, alongside pathogenic variants, CGH array and whole-exome sequencing inevitably identify many variants of uncertain significance, posing a great challenge to effective interpretation (Dan and Baxter 2014). In addition, customised gene panels are also becoming increasingly available. These allow screening of multiple known genes associated with a specific phenotype at much the same cost as single-gene analysis. Yet, because of decreasing costs, whole-exome sequencing is expected to replace CGH in many settings in the near future.

In this chapter, we review selected dysmorphic syndromes associated with genetic or chromosomal abnormalities. The somewhat arbitrary selection is based on epidemiology or clinical relevance in illustrating the complexity of neurological and behavioural phenotype and the diagnostic process.

**DOWN SYNDROME**

The presence of an abnormal number of chromosomes, or aneuploidy, in a cell often results in spontaneous termination of gestation, except with the sex chromosomes.

Down syndrome (OMIM#190685) or trisomy 21, i.e. an extra copy of chromosome 21, is the most common genetic cause of developmental intellectual impairment. The phenotype may comprise a variety of dysmorphic features including craniofacial features (Fig. 5.1), intellectual impairment, malformations such as congenital heart disease, and various other disorders such as immune deficits, Alzheimer disease and leukaemia. The original description was provided by British physician John Langdon Down in 1866 (Down 1866), and
the association with trisomy 21 was established in 1959 (Lejeune et al. 1959). A recent monograph reviewed Down syndrome comprehensively (Newton et al. 2016).

Epidemiology

It occurs sporadically in 1 in 700 live births, although the risk increases with maternal age. The birth prevalence has been decreasing due to more frequent elective pregnancy terminations after an antenatal diagnosis (de Graaf et al. 2015). Population prevalence, currently around 1 in 125, has increased dramatically over the past decades owing to longer life expectancy related to better access to medical care (Presson et al. 2013). Whereas in the 1990s few individuals survived beyond age 25, recent figures suggest that 20% of adults with Down syndrome are aged >55 years (Jensen and Bulova 2014).

Clinical Features

Cognitive impairment is mild in 40% of individuals, moderate in 35%, severe in about 25% and absent in around 1%. However, marked individual variability in skills is observed, and as always there are general limitations in using IQ to approach the actual functioning of individuals. Visuospatial perception (Vicari et al. 2005) is often better than verbal skills, although long-term (but not immediate) memory impairments have been documented in visual–object learning tasks (Jarrold et al. 2007). Receptive verbal language is typically better than expressive language, which shows particular deficits in phonology and syntax (Martin et al. 2009). Speech intelligibility is impaired by systematic sound errors, simplification patterns, speech apraxia and dysarthria. Syntax is typically more impaired than vocabulary for both receptive and expressive speech, to lower levels than expected given non-verbal cognitive ability. Specific verbal short-term memory deficits have also been documented (Laws 2002). The risk for developmental verbal impairment may be enhanced by conductive hearing loss, strongly associated with otitis media, which is found in almost all young children with Down syndrome. (In contrast sensorineural hearing loss is more frequent in adolescence and early adulthood.) Social skills are similar to typically developing children in preschool years. Later, patterns of interpersonal relationships remain parallel to typical development, and adults with Down syndrome generally show less antisocial behaviour and aggressiveness than many with other intellectual disabilities. Yet, social skills may markedly decline in patients who develop early onset Alzheimer disease, which is due to an additional copy of the gene encoding amyloid precursor protein and perhaps other genes. The prevalence of Alzheimer disease rises steeply from the fourth decade, reaching 250–800 per 1000 by age 60. The early symptoms seem to affect predominantly behaviour and personality, for example perseveration or apathy, rather than memory as in the general population, perhaps reflecting masking of memory deficits by presymptomatic cognitive impairment. However, early diagnosis is difficult for want of validated diagnostic tools for these patients (Ballard et al. 2016). Although this condition shows neuropsychological, neuroimaging and neuropathological findings that are very similar to late-onset Alzheimer disease, response to treatment, including cholinesterase inhibitors and the N-methyl-d-aspartate (NMDA)-receptor antagonist memantine, shows marked differences.

Hypotonia and associated ligamentous laxity are often marked, particularly in infancy. They contribute to postural control impairment (Rigoldi et al. 2011). Posterior ligamentous hyperlaxity may induce atlantoaxial subluxation, which can provoke cervical myelopathy.

Epileptic seizures occur in about 10% of individuals (Arya et al. 2011). Infantile spasms are frequent and seem to be better controlled by early, appropriate medication that in other patients with symptomatic infantile spasms (Arya et al. 2011). Other epileptic syndromes and seizure types may occur, particularly tonic–clonic and myoclonic seizures, which peak after the third decade. Many patients with dementia develop myoclonic seizures, predominantly on awakening, as part of a condition that has been termed ‘senile myoclonic epilepsy’ (De Simone et al. 2010), in which seizures appear to be associated with rapid cognitive decline.

Arterial ischaemic stroke (see Chapter 15) may occur in children secondary to infection or congenital heart disease. It commonly manifests with hemiparesis, but can also be caused by moyamoya disease, which occurs more frequently in Down syndrome than in the general paediatric population, although this association is poorly understood. Management of stroke or moyamoya in Down syndrome is not specific. Management in the acute phase of stroke is symptomatic, the use of intravenous tissue plasminogen activator being contraindiated because of the risk of intracranial bleeding (Hashimoto et al.
Factors, both immune mediated by T and B cells, and non-immune, such as preterm birth, congenital heart disease, anatomical features, gastro-oesophageal reflux and hypotonia.

Individuals with Down syndrome have increased susceptibility to infections, mainly respiratory, related to multiple anatomical features, gastro-oesophageal reflux and hypotonia.

Diagnostic Criteria and Testing
Clinical suspicion often arises at birth based on the phenotype, with findings such as hypotonia, upslanting palpebral fissures, epicanthal folds, overfolded helix, protruding tongue and a single palmar crease. When Down syndrome is suspected, conventional karyotyping will not only allow confirmation of the trisomy 21, but also determine if the extra chromosome 21 is part of a translocation (which a CGH array cannot identify). If a translocation is found, the karyotype of the parents should be obtained. If it is negative on lymphocytes, the possibility of mosaicism should be investigated.

Animal Models
Orthologues of the genes located on human chromosome 21 are located on three different chromosomes in mice (Davison et al. 2001). The Ts65Dn mouse (Reeves et al. 1995), which hosts duplicated parts of mouse chromosome 16 translocated to chromosome 17, results in trisomy for about half the human chromosome 21 genes. This mouse shows craniofacial abnormalities, learning deficits and neuropsychological features seen in Alzheimer disease.

Clinical Features
Most affected boys have absolute or relative macrocephaly. The face is typically long, with large, prominent ears. After puberty, macro-orchidism develops.

The disease presents with delayed developmental milestones and hypotonia, as well as a spectrum of intellectual disabilities ranging from mild to severe, with an average IQ of 40 in males. The cognitive profile may include impairment of language, executive function, visuospatial abilities, mathematics, and short-term and working memory, with a specifically impaired phonological loop (Baker et al. 2011).

More than 90% of males with fragile X syndrome show some behavioural features typically associated with autism, such as gaze avoidance, hyperarousal, perseverative speech or stereotyped behaviours (Bailey et al. 2000), and 60%, predominantly those with a low IQ, fulfil the diagnostic criteria for the ASD (Clifford et al. 2007; Harris et al. 2008). However, clinical differences between these males and males with non-syndromic ASD (see Chapter 29) have been noted (Thurman et al. 2015). Social affective symptoms, for example, are less severe at age 4 years in boys.
with fragile X syndrome, but worsen with age, perhaps in parallel with non-verbal IQ decline. Motor stereotypes typically include hand flapping. Tics are probably no more prevalent than in the general population (Kidd et al. 2014). Attention-deficit–hyperactivity disorder (ADHD) (see Chapter 30) is reported in up to 74% of males and 30% of females (Tranfaglia 2011) but the relevance of this diagnosis in neurodevelopmental genetic disorders has been questioned (Pelc and Dan 2008).

Seizures occur in 10–18% of patients, predominantly in males, slightly more in the group with ASD (Kidd et al. 2014). They may be partial or generalised, and commonly respond to pharmacological treatment.

Recurrent otitis media is more prevalent than in the general population, possibly because of anatomical factors, poor secretion control, oromotor hypotonia and dyspraxia.

**Genetics and Molecular Biology**

The syndrome results from mutations of the fragile X mental retardation 1 \((FMR1)\) gene, located on the X chromosome (D’Hulst and Kooy 2009). In close to 99% of individuals, these mutations consist of an increase (>200) in the number of CGG trinucleotide repeats in the gene’s 5’-untranslated region. However, they may also result from deletions or point mutations.

In unaffected individuals, \(FMR1\) contains around 30 CGG repeats. Repeats between 55 and 200 are regarded as a ‘premutation’. Boys with premutations are at increased risk of autistic features and seizures (Chonchaiya et al. 2012). Women who are carriers of a premutation may pass on a full mutation to their children, because the number of premutation CGG repeats often increases during meiosis.

In case of a full mutation (>200 repeats), the expanded repeat region is transcribed into the untranslated region of \(FMR1\) mRNA, which binds to the DNA repeat region, inactivating the \(FMR1\) gene (Colak et al. 2014).

The \(FMR1\) gene product appears to play a role in synaptic plasticity, for example in synaptic protein synthesis, interaction with metabotropic glutamate receptor signalling, mRNA transport and dendritic localisation, and selective inhibition of mRNA translation, but these have not been fully characterised. Abnormal synaptic plasticity would impair learning and memory processes.

Males with a full mutation almost always show signs of fragile X syndrome, whereas females with a full mutation generally show a penetrance of about 50% as a result of having another, unmutated \(FMR1\) allele. In females, the symptoms therefore range from mild to severe, although they are commonly less affected than males.

**Diagnostic Criteria and Testing**

Several authors have suggested use of clinical criteria to select patients for DNA testing. Scoring systems may include a long jaw and high, wide forehead, large and protruding ears, hyperextension of the metacarpophalangeal joint of the fifth digit, soft and velvety skin on the palms, macro-orchidism, initial shyness and lack of eye contact, followed by friendliness and echolalic speech, and a family history of intellectual disability (de Vries et al. 1999).

The diagnosis rests on the demonstration of a full mutation, i.e. >200 CGG repeats, of the \(FMR1\) gene. \(FMR1\) sequencing is necessary to identify fragile X syndrome due to deletions or missense mutations rather than excess CGG repeats.

Determination of the number of CGG repeats also allows for risk assessment of premutation carriers.

**Animal Models**

\(Fmr1\) knockout mouse models have provided insights into the role of the gene product in dendritic spine maturation, axonal arborisation synaptic plasticity and its regulation by metabotropic glutamate receptor signalling (Irwin et al. 2000; Bear et al. 2004). Drosophila models of mutant \(dfmr1\) have been designed for testing pharmacological approaches (McBride et al. 2013). However, clinical trials of drugs that were based on the hyperactive metabotropic glutamate receptor 5 were disappointing and are not being continued (Davenport et al. 2016).

**RETTSYNDROME**

Rett syndrome (OMIM#312750) is one of the most common causes of complex disability in girls. It is characterised by early neurological regression that severely affects motor, cognitive and communication skills, autonomic dysfunction and epilepsy. It was first recognised in 1954 by Andreas Rett, a Viennese paediatric neurologist (Ronen et al. 2009), who published his observations in an Austrian medical journal (Rett 1946). It was Bengt Hagberg from Sweden, however, who shared his own observations and revealed Rett syndrome to the international medical world in 1983 (Hagberg et al. 1983). In the late 1990s, \(MECP2\) mutations were identified (Amir et al. 1999), characterising Rett syndrome as a monogenic X-linked dominant neurodevelopmental disorder, the first to be related to a defective transcription of methylated DNA. A recent monograph addresses many aspects of the syndrome (Kaufmann et al. 2017).

**Epidemiology**

The prevalence of typical Rett syndrome (see below) is estimated at 1 in 10 000 women aged 32 years (Fehr et al. 2011). Almost all the causes are sporadic.
Clinical Features

Rett syndrome is characterised by neurological regression in infancy of motor, cognitive and communication skills, often leading to microcephaly, a delay in acquiring new skills, absence of speech, emergence of autistic features and loss of purposeful manipulation skills, replaced by distinctive stereotypical hand movements (Fig. 5.2). The time evolution of the phenotype has been delineated in a staging system (Engerström 1990).

Although retrospective analysis of home videos (Marschik et al. 2013) suggests that development may be suboptimal from the neonatal period, it is not obviously disturbed until a change in the girl’s behaviour during the early onset stagnation period (stage I), between 6 and 18 months of age. Sitting may emerge but not crawling or standing up, and bottom shuffling is very common. Transition to the rapid development period (stage II) occurs between age 1 and 4 years. Regression of acquired motor and communicative abilities is often sudden, evoking acute encephalopathy, but it may be gradual. Eye contact is preserved but babbling, interest in people and objects, words and fine motor skills are lost. This regression period is followed by the pseudo-stationary stage (stage III), during which walking may develop further but the loss of purposeful hand use is obvious, and stereotypical hand wringing or ‘hand washing’ becomes almost persistent in wakefulness. Breathing irregularities, sleep problems and epilepsy may also become more prominent in stage III. Dystonic asymmetrical posture leads to neurogenic scoliosis, often rapidly progressive, requiring surgical treatment. The feet and lower limbs are cold, with or without colour or atrophic changes. Motor regression slowly progresses in this stage, in contrast to a remarkably well-preserved ability to communicate, mainly with the eyes, and to learn. This stage can last for several decades. It is followed by the late motor deterioration (stage IV), when the individual becomes wheelchair dependent or shows muscle wasting and distal musculoskeletal deformity. Remarkable visual contact and eye-pointing behaviour remain present throughout this progression, and this must be recognised to foster communication and participation.

Other motor impairments include abnormal muscle tone (hypotonia, spasticity and dystonia may occur), ataxia and apraxia (Dan and Cheron 2008). Epilepsy occurs in up to 80% of patients. Many seizure types may be seen, including partial complex, generalised tonic–clonic, tonic and myoclonic seizures (Krajnc 2015). About a third of patients have drug-resistant epilepsy. Convulsive and non-convulsive status epilepticus may occur. Epilepsy tends to decrease after 20 years of age.

Autonomic manifestations include irregular breathing, reflecting abnormal brainstem control of carbon dioxide exhalation (Smeets et al. 2012). This may contribute to sudden death. Low resting cardiac vagal tone and weak vagal response to hyperventilation and breath-holding suggest inadequate parasympathetic control. There is a higher incidence of prolonged Q–T interval and diminished heart rate variability. Extremities tend to be cold as a result of poor perfusion related to altered autonomic control. Secondary vascular changes lead, in the long term, to atrophic changes in the lower limbs.

Genetics and Pathophysiology

Rett syndrome is caused by (mostly de novo) mutations in the MECP2 gene, located in the Xq28 region, usually on the paternal X chromosome. MECP2 encodes the methyl-CpG-binding protein MeCP2 (Amir et al. 1999). Mutations in the coding region can be identified in approximately 90% of patients with typical Rett syndrome (Philippe et al. 2006).

MeCP2 binds specifically to 5-methyl-cytosine throughout the genome, resulting in decacytation of histones and chromatin condensation, which leads to repression of transcription. MeCP2 is particularly abundant in the brain (Amir et al. 1999), where it is thought to suppress the transcription of other tissue-specific genes, the activity of which is not required. Loss of MeCP2 function may therefore lead to inappropriate overexpression of these other genes, with potentially damaging effect during CNS maturation (Ellaway and Christodoulou 2001). There is strong evidence that excitatory glutamate activity is too high in Rett syndrome, and some new therapies are being tested based on this (Johnston et al. 2015). Also trials of insulin-like growth factor are being conducted (Khwaja et al. 2014). However, the pathophysiology underlying the manifestations of Rett syndrome remains unclear.

Some variant phenotypes initially thought to be very similar to Rett syndrome are now known to be caused by mutations in other genes. The congenital variant is related to FOXG1 and the infantile seizure-onset variant (Hanefeld variant) is related to CDKL5. Other disorders with overbreathing include Pitt–Hopkins syndrome, related to TCF4 haploinsufficiency, and the CNTNAP2- and NRXN1-related disorders with severe intellectual disability, autism and breathing abnormalities, resembling the Pitt–Hopkins syndrome. The use of CGH array and whole-exome sequencing has provided new insights into Rett syndrome-like phenotypes (Lopes et al. 2016).
Rett syndrome was long thought to be lethal in hemizygous males. However, males with MECP2 mutations show the typical phenotype in case of somatic mosaicism or X polysomy. In other individuals, a variety of phenotypes can be seen from severe congenital encephalopathy, to severe intellectual disability with various neurological symptoms, to isolated mild cognitive impairment.

**Diagnostic Criteria and Testing**
Clinical diagnostic criteria have been suggested for Rett syndrome (Neul et al. 2010). The diagnosis should be made in the presence of a period of regression followed by recovery or stabilisation, and all the following main criteria: loss of purposeful hand use and spoken language; impaired (dyspraxic) or absent gait; and stereotypical hand movements such as hand wringing, clapping, mouthing and rubbing.

These features characterise typical Rett syndrome. Diagnosis of atypical or variant Rett syndrome can be made if only two of the main criteria are present together with at least five of the following supportive criteria: intense eye contact or eye-pointing communication, diminished response to painful stimuli, breathing disturbances or bruxism when awake, inappropriate screaming or laughing, impaired sleep, abnormal muscle tone, growth retardation, scoliosis, small cold hands and feet, and peripheral vasomotor disturbances.

Analysis of the coding regions of the MECP2 gene using sequencing techniques yields >90% mutation detection in typical Rett syndrome. Additional analysis using multiplex ligation-dependent probe amplification raises the detection rate to >95% by highlighting gross rearrangements in the coding region (e.g. deletions or duplications such as those involving exons 3 and 4).

In atypical Rett syndrome, the rate of detectable mutations in MECP2 is lower, and in some of these patients the cause is another genetic abnormality (Lopes et al. 2016).

Among other investigations commonly carried out, EEG is usually normal during stage I but background activity slowing and epileptiform discharges occur in later stages (Glaze 2005), none of these changes being specific.

**Animal Models**
Mecp2−/− female mice, which are homologous to human patients with Rett syndrome (Lombardi et al. 2015), show no abnormalities when they are young (they are even fertile), but later they show hindlimb clasping and breathing irregularities. There seems to be an effect of MeCP2 dosage. Half the MeCP2 protein expression is associated with altered social behaviour (Samaco et al. 2008). Conversely, a twofold increase in Mecp2 expression results in a progressive neurological disease with cognitive impairment and social problems, reminiscent of the human condition associated with MECP2 duplication (Van Esch et al. 2005). Promising results of targeted-therapy in mouse models may soon have an application in Rett syndrome (Johnston et al. 2015).

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**ANGELMAN SYNDROME**

Angelman syndrome (OMIM#105830) is characterised by developmental delay with intellectual impairment, a typical happy, exuberant behaviour, absent speech contrasting with eagerness for social interaction, motor impairment and epilepsy. It is caused by a lack of UBE3A expression, which normally occurs in the brain through the chromosome 15 inherited from the mother. The syndrome was first described in 1965 by British paediatrician Harry Angelman in three unrelated patients, whom he described as ‘puppet children’ in an attempt to encapsulate their behaviour (Angelman 1965).

In the 1980s, distinctive non-epileptic rhythmic EEG features were documented, and abnormalities of chromosome 15q11-q13 similar to those found in Prader–Willi syndrome were described; the factor determining the phenotypic outcome was the parental origin of the chromosome defect, i.e. genomic imprinting. In 1997, the absence of expression of the UBE3A gene was recognised as the single cause of Angelman syndrome. A monograph covers many aspects of the syndrome (Dan 2008).

**Epidemiology**
Prevalence estimates are between 1 in 10,000 and 1 in 0,000 (Petersen et al. 1995; Thomson et al. 2006). The vast majority of cases are sporadic. Familial recurrence depends on the underlying molecular mechanism. The recurrence risk is very low (<1%) where there is a new 15q11-q13 deletion or uniparental disomy. Situations involving UBE3A gene mutations or imprinting defects may be more complex, because members of the mother’s extended family are also at increased risk. Most mutations occur anew and are associated with a very low recurrence risk, although mutations inherited from the mother are associated with a 50% recurrence risk.

**Clinical Features**
All individuals have developmental delay with severely impaired cognitive skills, although accurate assessment is often difficult because of confounding factors, such as adaptive skills, and behavioural and motor features. Intellectual disability is statistically more severe in individuals with a chromosome 15q11-q13 deletion, but abilities show a great deal of overlap across the different molecular classes (Mertz et al. 2014). Speech impairment is consistently severe, presumably due to combined oral dyspraxia, pragmatic factors and intellectual disability. Receptive verbal language and non-verbal language are relatively preserved. In addition to pointing, nodding and other gestures, expressive skills typically include facial expressions,
although a bias towards positive expressions is possible, limiting expressive selectivity. Frequent smiling and laughing are prominent (Adams et al., 2015), which correlate with the context but may be pervasive and increase with anxiety. The ‘happy’ disposition (Fig. 5.3) is accompanied by a markedly positive interpersonal bias, gregariousness and social disinhibition, which persist in adulthood. However, social adaptation may be impaired because of poor detection and respect of emotional and social signals. Aggressive behaviour may be seen, sometimes as grabs or rough hugs. Excessive sociability may have a role in the development and maintenance of these behaviours through proactive attention seeking. This has significant implications for clinical practice and behavioural intervention.

Hypermotor, exuberant behaviour is almost persistent in childhood, but decreases later, often giving way to reluctance to exercise in adolescence and adulthood. Impulsivity, distractibility and short attention span occur at similar frequencies to other conditions with moderate-to-severe intellectual disability (Barry et al., 2005), although clinical characteristics of ADHD (see Chapter 34) are not discriminating features of Angelman syndrome, so this label is misleading in the context of counselling, management and research issues (Pelc and Dan, 2008). Motor stereotypes are very frequent. No single pattern appears to be specific, or even evocative, despite classic emphasis on hand flapping, which is frequent in other syndromes (e.g., fragile X syndrome) and non-syndromic intellectual disability, not to mention typically developing children. Although these stereotypes may appear similar to those seen in the ASD (see Chapter 29), they correlate with a low developmental profile rather than being specific of autism (Bonati et al., 2007).

Sleep problems are seen in up to 90% of patients, including difficulties in initiating or maintaining sleep, irregular sleep–wake cycles, and sleep-related seizures or movement disorders, none being distinctive (Pelc et al., 2008a). As in other neurodevelopmental conditions, they appear to be more severe in early childhood.

Muscle tone abnormalities include moderate axial and limb hypotonia, or sometimes distal spasticity (Dan and Cheron, 2008). Despite varying degrees of ataxia, most children develop independent walking after age 3 or 4 years. Gait is distinctive, with a wide base, lower limb extension and lateral rotation, and associated elbow flexion and wrist pronation. A crouch-gait pattern may also be seen, as well as dynamic equinus or equinovarus, potentially leading to fixed contractions as in spastic cerebral palsy. Mild action tremor is common in children and adults. Day-long clusters of disabling, prominent, quasi-clonic myoclonus, or resting tremor of unclear pathophysiology, may occur in adolescents or adults. Response to treatment, whether antiepileptic or modulating adrenergic or dopaminergic pathways, is often poor.

More than 90% of patients have epilepsy, with onset often between age 1 and 3 years (Pelc et al., 2008b; Leyser et al., 2014). Many seizure types, both generalised and focal, have been reported, including epileptic spasms, myoclonic absences and myoclonic, atonic, tonic and tonic–clonic seizures, but atypical absences and myoclonic seizures have been particularly emphasised. As in other developmental conditions with epilepsy, the seizure disorder often improves in late childhood, although epilepsy can persist or reappear in adulthood and be difficult to control. Both convulsive and non-convulsive status epilepticus may occur. The latter is particularly common during childhood, but it can occur in infancy and adulthood.

Genetics and Molecular Biology

Angelman syndrome illustrates genomic imprinting, in which expression of imprinted genes is monoallelic and dependent on the parental origin (but not on the sex of the offspring). It is caused by lack of expression of the imprinted UBE3A gene, located on the long arm of chromosome 15; this gene is specifically imprinted in the brain, where it is expressed through the allele inherited from the mother with silencing of the paternal allele. The role of UBE3A in the pathophysiology of the phenotype is currently unclear. The gene product, UBE3A, is a ubiquitin ligase involved in labelling proteins for trafficking to their proper destinations, for example, selective destruction along the ubiquitin–proteasome pathway. Several potentially relevant UBE3A substrates have been identified, including activity-regulated, cytoskeleton-associated protein (Arc) and ephexin-5, which have roles in synaptic plasticity. Effects on inhibitory (chiefly GABAergic) neurons have been documented (Dan and Boyd, 2003; Judson et al., 2016; Santin and Klann, 2016).
In about 70% of patients, lack of UBE3A expression is caused by a new 15q11-q13 deletion on the chromosome 15 inherited from the mother. In 10% of patients, there is a mutation in the maternal UBE3A gene. Most of such mutations occur anew, but around 20% are carried by the mother. The 15q11-q13 deletions and UBE3A mutations are commonly associated with a more severe phenotype than other molecular classes. About 5% of patients have an imprinting defect, resulting in a lack of the typical maternal pattern of DNA methylation. Imprinting defects may be caused by (possibly inherited) mutations in the ‘imprinting centre’, a small region in chromosome 15q11-q13 that regulates gene expression. Fewer still have paternal uniparental disomy, i.e. both copies of chromosome 15 inherited from the father and none from the mother. In very rare cases, maternal UBE3A gene inactivation results from chromosome 15 rearrangements. Finally, in less than 10% with a typical phenotype for Angelman syndrome, no genetic abnormalities can be found.

Diagnostic Criteria and Testing

The clinical diagnosis is based on a set of physical and behavioural features (Williams et al. 2006). The consistent features comprise functionally severe developmental delay, happy, excitable demeanour with frequent laughter and smiling, severe speech impairment and motor disturbances, usually mild ataxia or tremor. Frequent features, present in more than 80% of patients, include delayed, disproportionate growth in head circumference, usually resulting in microcephaly by 2 years of age, epilepsy and characteristic non-epileptic EEG rhythmic patterns. These patterns may contribute to diagnosis, particularly before the clinical features become obvious (Boyd et al. 1988; Clayton-Smith and Laan 2003; Leyser et al. 2014). Features seen in more than 20% of patients include prognathia, tongue thrusting, feeding problems in infancy, excessive mouthing behaviours and abnormal food-related behaviours with obesity later in childhood, fascination with water, scoliosis, and hypopigmented skin, hair and eyes (the last only in those with 15q11-q13 deletions, as in Prader–Willi syndrome, due to hemizygosity of the OCA2 gene, the mutations of which are known to cause oculocutaneous albinism type 2).

Genetic confirmation is important for adequate counseling, because the recurrence risk depends on the underlying genetic mechanism. Deletions, which are usually not detected by a routine chromosome study, can be identified by CGH array analysis, or multiplex ligation-dependent probe amplification (MLPA), which on top of microdeletions will also detect uniparental disomy. UBE3A gene sequence analysis can detect mutations. Imprinting defects may be detected by DNA-methylation analysis, but additional testing is required to exclude a deletion. Uniparental disomy can be detected using DNA-methylation analysis or DNA-polymerase testing. Genetically distinct conditions, including Rett syndrome, may show some phenotypical overlapping with Angelman syndrome (Luk 2016).

The value of EEG has been underlined above. There have been neuroimaging reports of abnormal myelination, which require confirmation in larger series.

Animal Models

Animal models of the different mechanisms underlying the syndrome have facilitated the progress in understanding the molecular pathogenesis and provided bases for experimental attempts at restoring functions disrupted in these animals, hopefully leading to effective therapeutic strategies. Most current murine models replicate features described in patients (Jana 2012). Drosophila models have also been promising.

Prader–Willi syndrome (OMIM#176270) is characterised by typical facial, cognitive, behavioural, neurological, endocrine and psychiatric features. It was first described in 1956 by Swiss paediatricians Andrea Prader, Heinrich Willi and Alexis Labhard, based on nine children with small stature, small hands and feet, a history of neonatal hypotonia, early onset severe obesity, insatiable hunger and intellectual disability (Prader et al. 1956). Genetic findings in the late 1980s revealed it as the first human condition related to genomic imprinting. Different mechanisms can lead to the absence of expression of the paternally imprinted genes, including SNRPN, in the 15q11-q13 region.

Epidemiology

Prader–Willi syndrome occurs in about 1 in 15000–30000 individuals. The prevalence is high among newborn infants with hypotonia, being higher than 10% in some series (Tuysuz et al. 2014).

Clinical Features

The early presentation includes reduced fetal movements, neonatal hypotonia, poor sucking and feeding difficulties, leading to initial failure to thrive. The face commonly shows a narrow forehead, almond-shaped and upslanting palpebral fissures, and full cheeks.

Gross motor development and language are delayed, (e.g. sitting achieved around 12 months, walking around 24 months, first words around 2 years). Most patients have mild cognitive impairment (IQ 60–70), although the range goes from severe impairment to normal intelligence. Expressive and receptive language abilities are typically lower than non-verbal intelligence, with some group differences according
to the molecular mechanism underlying the syndrome (Dimitropoulos et al. 2013). Problems have been described in interpreting emotional facial expressions, understanding personal space and in theory of mind development (Rice and Einfeld 2015).

The behavioural phenotype includes temper tantrums, stubbornness, obsessive–compulsive behaviours, skin picking, difficulty with changes and the hallmark abnormal food-related behaviour: an extreme unsatisfied drive to consume food, (i.e. hyperphagia). Children start developing an insatiable appetite with rather aggressive food-seeking behaviour at around 8 years (3–15 years) of age. This behaviour results in obesity and lasts into adulthood, when it usually improves significantly. Obesity is a major cause of morbidity and mortality in adulthood. Sleep disorders include excessive obstructive and central sleep apnoea, hypoventilation, abnormal circadian rhythms in rapid eye movement (REM) sleep, reduced REM latency and abnormal response to hypercapnia, as well as excessive daytime sleepiness. Obesity can worsen the sleep disorder. An increased risk of psychosis has been particularly highlighted in those with maternal uniparental disomy (Rice and Einfeld 2015).

Another characteristic feature is hypogonadism of hypothalamic origin, with genital hypoplasia, delayed or incomplete pubertal development, and infertility. Short stature is due to growth hormone insufficiency and exacerbated by the lack of a pubertal growth spurt. Osteoporosis and increased fracture risk may be complications of hypogonadism. Obesity caused by hyperphagia and hypometabolism (secondary to hypopituitarism) is a risk factor for cardiorespiratory failure, sleep apnoea and type 2 diabetes mellitus.

Growth hormone therapy has been shown to improve a number of phenotypic features in individuals with Prader–Willi syndrome (Fig. 5.4), including decreasing body fat, increasing muscle mass, and improving muscle strength and cognitive functioning (Grugni 2016).

Genetics and Molecular Biology

Three main molecular mechanisms cause Prader–Willi syndrome through lack of expression of the imprinted genes that are normally expressed from a region on the chromosome 15 inherited from the father. This 15q11-q13 region also contains a number of genes that are expressed only through the maternal copy of the chromosome. Therefore, deletions in this region result in Prader–Willi syndrome if they involve the paternal copy and in Angelman syndrome if they involve the maternal copy. A mother with Prader–Willi syndrome can thus have a child with Angelman syndrome (Schulze et al. 1992).

In about 70% of cases the mechanism is a new 15q11-q13 deletion. A maternal uniparental disomy of chromosome 15 is found in >25% of patients, resulting in silencing imprinted genes. Maternal uniparental disomy is most commonly due to maternal meiotic non-disjunction followed by mitotic loss of the paternal chromosome 15. In <5%, the syndrome is caused by an imprinting defect, which is commonly regarded as a chance error occurring during spermatogenesis, although it may result from a microdeletion in the Prader–Willi syndrome imprinting centre region at the 5’ end of the (paternally expressed) SNRPN gene, also located in the 15q11-q13 region. Other nearby (mostly paternally expressed) genes may contribute to the phenotype, such as SNORD116.

Diagnostic Criteria and Testing

Diagnostic criteria have been suggested, based on points attributed to major, minor and supportive features (Gunay-Aygün et al. 2001). Major criteria include characteristic facial features, neonatal hypotonia, developmental delay, feeding problems in infancy, rapid weight gain between age 1 and 6 years, hypogonadism and 15q11-15q13 deletion. Minor criteria include decreased fetal movements, weak cry in infancy, sleep disturbances, small hands and feet, and behavioural problems such as temper tantrums, skin picking, obsessive–compulsive or oppositional behaviour and stubbornness. There are also supportive findings, such as reduced response to pain, altered temperature control, scoliosis and/or kyphosis, early adrenarche, osteoporosis and unusual skill with jigsaw puzzles.

Multiplex ligation-dependent probe amplification has become standard for identifying 15q11-q13 deletion, uniparental disomy and imprinting defect. Deletion is now rarely diagnosed using an SNRPN fluorescence in situ hybridisation (FISH) probe. Chromosome analysis should be included in testing when a deletion is found, because occasionally this may result from a chromosomal translocation.

In the neonatal period, the differential diagnosis of severe hypotonia includes spinal muscular atrophy and myotonic dystrophy type 1 (see Chapter 26).

Animal Models

There are mouse models, based on large deletions, that show some similarity with the most common human deletions, and

Figure 5.4 A 7-year-old boy with Prader–Willi syndrome treated with growth hormone. Note the narrow forehead, almond-shaped eyes, full cheeks and muscle wasting but no obesity. (Courtesy of Dr Anne Monier, Hôpital Universitaire des Enfants Reine Fabiola, Brussels)
THE 22q11.2 DELETION SYNDROME

The 22q11.2 deletion syndrome (OMIM#188400) is one of the most common multiple anomaly syndromes. It is also known as DiGeorge sequence, velocardiofacial syndrome, Shprintzen syndrome, Sedláčková syndrome and CATCH22 (cardiac abnormality/abnormal facies, T-cell deficit due to thymic hypoplasia, cleft palate and hypocalcaemia caused by hypoparathyroidism from the 22q11 deletion). The pattern of inheritance was confirmed to be autosomal dominant in the early 1980s (Shprintzen et al. 1981), and the causative microdeletion was identified in the early 1990s. The expression is highly variable. The clinical features can involve many systems and organs, resulting in craniofacial features, palatal defects, congenital heart defects, hypocalcaemia (resulting from parathyroid hypoplasia), immunodeficiency, cognitive impairment and various neuropsychiatric disorders.

Epidemiology

The prevalence based laboratory-confirmed 22q11.2 deletion is approximately 1 in 6000 live births (Bottro et al. 2003). As in other developmental disorders, some clinical findings do not appear until later in life. It must also be noted that some phenotypic conditions are incompatible with life, for example, pulmonary atresia associated with a major heart defect.

Clinical Features

More than 180 distinct clinical phenotypes of the 22q11.2 deletion syndrome have been described, with features involving almost every organ system and developmental function. The neurocognitive profile is also highly variable (Shprintzen 2008). Early hypotonia and developmental delay are often present. Speech impairment is frequent, particularly hypernasal speech and severe articulation impairment. Speech onset is usually mildly delayed. Receptive language abilities are often better than expressive ones (Golding-Kushner et al. 1985), although part of the expressive disorders are probably amenable to effective remediation. Most patients have borderline cognitive abilities (IQ 70–84), and about a third have mild-to-moderate intellectual disability (Swilien and McDonald-McGinn 2015). Individuals have an increased risk for several psychiatric disorders including ADHD (see Chapter 30), ASD (see Chapter 33), anxiety disorders and psychotic disorders.

Congenital heart disease occurs in about 70% of individuals, particularly conotruncal (i.e. bulbus cordis) heart anomalies, including interrupted aortic arch, persistent truncus arteriosus, tetralogy of Fallot and ventricular septal defects. Vascular anomalies may involve chest, neck and brain arteries. Palatal anomalies such as submucous and occult submucous cleft palate are also common, resulting in hypernasal speech. Other possible abnormalities that have been reported in the context of the syndrome include brain, spinal, ocular, skeletal (including cranial, vertebral and limb) and renal anomalies, as well as increased platelet size, hyperthyroidism and hypoparathyroidism.

Early feeding problems can result from hypotonia, congenital heart disease, endocrine disorders, and airway obstruction secondary to the combination of retrognathia and hypotonia.

Genetics and Molecular Biology

In the large majority of patients, the 22q11 deletion involves more than 40 genes. The syndrome is commonly regarded as a contiguous gene syndrome. Among the possibly relevant genes, TUPLE1 has been suggested as a candidate for explaining a number of features, as it encodes a transcription factor expressed at a critical period in the development of the outflow tract of the heart and the neural crest-derived aspects of the face and upper thorax (Halford et al. 1993). Hemizygosity for the COMT gene has also attracted attention, because its product, catechol-O-methyltransferase, is one of the enzymes that degrade catecholamines such as dopamine, adrenaline and noradrenaline. However, no (or little) effect of COMT polymorphism has been demonstrated on IQ and various aspects of executive function in children with 22q11.2 deletion syndrome (Glaser et al. 2006).

In addition, the penetrance of the deletion as a facilitator for the emergence of the defects has been suggested as depending on copy-number changes outside the deleted region, according to a ‘two-hit’ model where the deleted region would act as a modifier at the level of the affected organ systems (Hiroi et al. 2013; Mlynarski et al. 2015).

Diagnostic Criteria and Testing

As a result of the extreme variability in phenotypic expression of 22q11.2 deletion syndrome, the reliability of diagnostic criteria or a probability approach has been disputed (Shprintzen 2008). Whatever the presentation, the diagnosis relies on demonstrating a 22q11.2 deletion. CGH has become the first-choice diagnostic test, although other testing may be preferred when a fast confirmation of the clinical diagnosis is required. This may be raised, for example, by the presence of interrupted aortic arch, tetralogy of Fallot and truncus arteriosus in newborn infants. Hypernasal speech or cleft palate may also raise suspicion if associated with other anomalies in the
context of a multiple anomaly presentation. Features such as characteristic ears, asymmetrical facial animation, hypotonia or any of the other anomalies consistent with the syndrome would also be evocative.

Specific testing is indicated on the basis of the clinical manifestations. MRI may show reductions in both grey and white matter volumes, as well as abnormalities in the corpus callosum, amygdala, caudate nucleus and temporoparietal regions of the brain (Shprintzen 2008).

**Animal Models**

The syntenic region on murine chromosome 16 shows a high degree of conservation with respect to the human 22q11.2 region. Mouse models, whether based on deletions or single gene inactivation, have been used to characterise molecular function of a number of genes in 22q11.2 and in the study of genotype–phenotype correlations (Hiroi et al. 2013). Zebrafish, drosophila and worm models could also prove useful in studying these molecular mechanisms (Guna et al. 2015).

**WILLIAMS SYNDROME**

Williams syndrome (or Williams–Beuren syndrome, OMIM #194050) also affects multiple systems, resulting in distinctive facial features, and a characteristic behavioural phenotype that includes cognitive impairment, pulmonary artery or aortic stenosis, and infantile hypercalcaemia. Several of these features were described as distinct entities (Fanconi et al. 1952; Williams et al. 1961; Beuren et al. 1962) before the syndrome was recognised in the early 1960s. Williams syndrome is associated with a new chromosome 7q11.23 deletion.

**Epidemiology**

Williams syndrome is almost always sporadic, with a prevalence around 1 in 7500 (Strømme et al. 2002).

**Clinical Features**

In young children the face typically shows a wide forehead, periorbital fullness, depressed nasal bridge and bulbous nasal tip, full cheeks, a long philtrum, a wide mouth and a thick lower lip (Fig. 5.5). Older children and adults usually have a thinner face but still show the full nasal tip, malar flattening, wide mouth and thick lips.

Children present with developmental delay. Hypotonia may be marked in infancy and early childhood. Later in life, hyperreflexia, clonus, extrapyramidal signs and cerebellar signs commonly occur. Average full-scale IQ is 55, but a distinctive distribution of cognitive abilities is often (but not always) found, with better language and face processing than visuospatial, memory and number processing. This discrepancy emerges gradually, and performance is often regarded as atypical rather than impaired, suggesting weak central coherence (Van Herwegen 2015) making global processing of information difficult. Sensorineural hearing loss at high frequencies is common. The behavioural phenotype includes overfriendliness and empathy, attention problems, anxiety and sleep disturbances (Mervis et al. 2000).

Cardiovascular problems include elastin arteriopathy, supravalvular aortic stenosis is found in about 70% of patients. Arterial stenosis can be isolated or occur in multiple locations (aortic arch, descending aorta, and intracranial, coronary, renal, mesenteric and pulmonary arteries). Sleep disturbances are common. There is also an increased risk for urinary tract structural anomalies and diverticulosis. Hypertension may occur; the pathophysiology is often unclear. Hypercalcaemia may occur, which is often asymptomatic and commonly resolves in the first few years of life. Eventual manifestations may include irritability and gastrointestinal symptoms. Unrelated feeding difficulties and failure to thrive may also occur. Joint laxity in early childhood may be followed by gradual tightening of hamstrings and heel cords (Gagliardi et al. 1997).

**Genetics and Molecular Biology**

Chromosome 7q11.23 deletions (or rarely duplications or inversions) result from meiotic recombination between highly similar, duplicated sequences. The deletion (0.2–2.5 Mb) associated with Williams syndrome always induces ELN (elastin gene) haploinsufficiency. Longer deletions are associated with a more severe phenotype. Those with deletions including
MAGI2 have a higher risk for severe cognitive impairment and infantile spasms (Marshall et al. 2008). Similar to most conditions in this chapter, CGH has acquired a major role in the diagnostic approach.

Recent findings of markedly altered DNA methylation in Williams syndrome suggested that epigenetic mechanisms related to binding and chromatin regulation probably contribute to the complex neurological phenotype (Strong et al. 2015).

### Diagnostic Criteria and Testing

Clinical diagnostic criteria have been suggested using scores based on the presence of signs relating to growth, facial features, behaviour and development, cardiovascular abnormalities, connective tissue-related problems and calcium studies (Committee on Genetics, American Academy of Pediatrics 2001). They include failure to thrive and gastrointestinal symptoms, a number of facial characteristics, supravalvular aortic stenosis, peripheral pulmonary artery stenosis, congenital heart disease, hypertension, hoarse voice, joint limitation or laxity, inguinal hernia, hypercalcaemia and hypercalciuria. However, more than 99% of patients who fulfil these criteria have a 7q11.23 deletion, so that the diagnosis currently relies on the demonstration of an abnormality in this region (Committee on Genetics, American Academy of Pediatrics 2001). The deletion can be detected by FISH, MLPA and deletion or duplication by chromosome microarray.

### Animal Models

A mouse model with a deletion of the whole region analogous to that commonly deleted in Williams syndrome shows growth retardation, cardiovascular abnormalities, increased sociability, anxiety and motor coordination deficits (Li et al. 2009). It also shows reduced brain volume and increased density of neuronal packing in layer V of the somatosensory cortex, possibly correlating with that observed in layer IV of the visual cortex in Williams syndrome (Galaburda et al. 2002). Models with targeted inactivation of single genes such as analogues to ELN, BAZ1B, CLIP2 and GTF2IRD1 are potentially informative about their contribution to the syndrome, although hemizygosity for some of these genes in mice does not necessarily imply similar levels of haploinsufficiency to humans (Osborne 2010). These models are also being used for testing therapeutic interventions.

### CORNELIA DE LANGE SYNDROME

Cornelia de Lange syndrome (OMIM#122470) includes distinctive facial features, intellectual impairment, growth retardation and organ anomalies. It was first extensively described by the Dutch paediatrician Cornelia de Lange in 1933 (de Lange 1933), although she acknowledged Franz Bruck’s 1889 report as the original description, and German physician Winfried Brachmann published an independent report in 1916, hence the alternative eponyms Bruck–de Lange syndrome and Brachmann–de Lange syndrome. It is caused by (usually de novo) mutations in NIPBL or other genes encoding components of cohesin, which has a role in cell division.

### Epidemiology

Cornelia de Lange syndrome is typically sporadic. In familial cases, the phenotype seems to be consistent within a family. A large European population-based study found a prevalence of 1 in 81000 live births for the classic form and estimated the overall prevalence between 1 in 45000 and 1 in 65000 (Baricic et al. 2008).

### Clinical Features

The phenotypic expression is variable. It is typically characterised by multiple malformations including cardiac, gastrointestinal and musculoskeletal systems, characteristic facial features, hirsutism, pre- and postnatal growth retardation (affecting weight, height and head circumference), developmental delay and a peculiar behavioural phenotype.

The craniofacial features are pathognomonic. They include micro-brachycephaly, webbed, short neck and low hairline. The eyebrows are bushy and arched (possibly compensatory to ptosis), joining at the midline (i.e. synophrys). The eyelashes are long and curly. The palpebral fissures are narrow. The ears are thick, dysplastic and low set. The nose is short with nasal bridge depression. The midface is flat with a long, smooth philtrum, thin upper lip and down-turned corners of the mouth (described by some as a carp mouth). High-arched palate, widely spaced teeth and micrognathia are common.

In about 70% of patients, intellectual disability is profound or severe (Oliver et al. 2008), but the range of intellectual functioning is wide and there are individuals with no cognitive impairment. Impairments are typically more marked in expressive than receptive communication. Communication, mood and socialisation skills tend to worsen with age (Srivastava et al. 2014). The behavioural phenotype includes behaviours seen along the autism spectrum, although eye contact is commonly better preserved and there are often fewer stereotypes than in non-syndromic autism. Tools developed for symptom evaluation in ASD have been useful in Cornelia de Lange syndrome, including the Childhood Autism Rating...
Scale (CARS), Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview, Revised (ADI-R) (Parisi et al. 2015). Compulsive, impulsive behaviour and self-injury are also at the forefront (Oliver et al. 2008).

Epilepsy occurs in about 20% of children. Partial seizures are the most common seizure type. In most patients, epilepsy shows a good response to pharmacological treatment, often valproate monotherapy (Verrotti et al. 2013).

Growth retardation starts in the antenatal period and results in proportionate small stature, often below the 5th centile (Kline et al. 1993). The hands and feet are small. The first metacarpal shows disproportionate shortening, the thumb is inserted proximally, and brachydactyly and fifth finger clinodactyly are frequent. Scoliosis may develop by age 10 years. However, patients rarely require orthopaedic surgical intervention.

Genetics and Molecular Biology
To date, mutations in five genes have been associated with Cornelia de Lange syndrome. They can be found in about 70% of patients with a clinical diagnosis and the following are the five genes involved: NIPBL on chromosome 5, RAD21 on chromosome 8, SMC3 on chromosome 10 and SMC1A3 and HDAC8 both on the X chromosome. All these genes are involved in the structure or the regulation of the cohesin complex, which regulates the separation of sister chromatids during cell division. Several proteins of this complex are also involved in other DNA-related processes, such as double-strand DNA break repair and regulation of transcription. The understanding of how perturbation of cohesin may lead to the Cornelia de Lange syndrome needs to be integrated in a wider perspective of ‘cohesinopathies’, which entail an increasing number of human developmental disorders, such as Roberts syndrome (characterised by a pattern of craniofacial and limb malformations) and forms of cancer (Liu and Krantz 2009).

Diagnostic Criteria and Testing
Diagnosis of Cornelia de Lange syndrome is based on clinical criteria which include a severity scoring system revised by Kline et al. (2007). The clinical diagnosis rests on the presence of synophrys, with three or more secondary criteria relating to craniofacial features, and involvement of other system categories, including growth, development and behaviour. Molecular confirmation of the diagnosis can be obtained by using a gene panel that includes NIPBL, SMC1A, SMC3 and MAPL, possibly followed by CGH. When mutations cannot be detected from lymphocytes, somatic mosaicism can be suspected, because this has been found in about 25% of patients (Huismans et al. 2013). Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Animal Models
There is active research on mouse and zebrafish models of Nipbl haploinsufficiency, with a special focus on small changes in the expression of many other genes and their relationship to phenotypic abnormalities.
Genetics and Molecular Biology

Noonan syndrome may be sporadic or follow an autosomal dominant pattern of inheritance. About half the patients have a (missense) mutation in the \( PTPN11 \) gene, resulting in gain of function (Tartaglia et al. 2001). The gene product is involved in intracellular signalling cascades along the Ras-MAPK pathway, downstream of receptors for cytokines, growth factors and hormones, and is active in a number of developmental processes. Mutations in a number of genes can also cause the syndrome, (e.g. \( KRAS \) and \( SOS1 \)), which also have a role in the Ras-MAPK pathway.

Diagnostic Criteria and Testing

Clinical diagnostic criteria were suggested before causative mutations were discovered (van der Burgt et al. 1994) but it is still useful for identifying patients for genetic testing. The scoring system takes into account the typical facial dysmorphology, cardiac abnormalities such as pulmonary stenosis or hypertrophic obstructive cardiomyopathy, short stature, pec­torus carinatum or excavatum, the family history, intellectual disability, cryptorchidism and lymphatic dysplasia. \( PTPN11 \) mutation should be looked for. In \( PTPN11 \) mutation-negative cases, other mutations along the Ras-MAPK pathway can be searched, for example, by means of dedicated gene panels.

Animal Models

Mouse models have been engineered, most of them based on \( PTPN11 \) mutations. Insights have thus been gained into craniofacial, cardiac and growth abnormalities.

TURNER SYNDROME

Turner syndrome is the only known viable chromosomal monosomy. It is characterised by the complete or partial (small arm) absence of an X chromosome. It is the most common chromosomal abnormality in females. The phenotype includes characteristic dysmorphic features described in 1938 by the American endocrinologist Henry Turner (Turner 1938). German paediatrician Otto Ullrich had reported on a girl in 1930. The 45,XO karyotype was demonstrated in 1959.

Epidemiology

The incidence is about 1 in 2500 female births.

Clinical Features

The main characteristic signs are present from early in life, most of them at birth. They include short stature, scoliosis, low posterior hairline, hypertelorism, high-arched palate, micrognathia, short and webbed neck, lymphoedema of the hands and feet, fourth/fifth metacarpal or metatarsal hypoplasia and hypoplastic nails. There is also gonadal dysgenesis with hypogonadism. Cardiac malformations include coarctation of the aorta and ventricular septal defects. The risk for stroke is increased. Renal anomalies include horseshoe kidney, urethral duplication and unilateral kidney agenesis. Additional health conditions may comprise hearing and visual impairment, arterial hypertension, osteoporosis, obesity and diabetes mellitus (Santos et al. 2012). IQ is usually normal, but visuospatial and mathematical skills are often impaired (Knickmeyer 2012). Epilepsy is rare. There is an increased risk for psychiatric disorders, such as ASD, anxiety disorders and schizophrenia. However, many women with Turner syndrome marry and lead well-adjusted lives in adulthood.

Genetics and Molecular Biology

It seems that deletion of the short arm of the X chromosome is sufficient to result in Turner syndrome. Monosomy of the X chromosome is found in about 50% of individuals with Turner syndrome. The other cases may be caused by mosaicism or structural alterations of the X chromosome, including isochromosome, i.e. one rearranged X chromosome containing two mirror images of the long arm, whereas the short arm is missing.

Individuals with Turner syndrome who have a maternally inherited X chromosome tend to have more social interaction problems than those whose X chromosome is paternally derived (Skuse et al. 1997).

Among the genes that might account for phenotypic features, \( SHOX \) (short stature homoeobox gene), a transcription factor, may relate to short stature and some limb abnormalities (Binder 2011). Other regions in Xq may cause ovarian failure, including the \( FMR1 \) and \( BMP15 \) genes.

Diagnosis

The diagnosis can be confirmed by CGH array analysis, which can identify whole X-chromosome loss as well as small Xp deletions. Conventional karyotyping can be complementary to characterise possible chromosomal rearrangement, or detect low mosaicism (if a sufficient number of cells are analysed). Hormonal dosages may also be useful.

Animal Models

Models based on the 39,XO mouse, in which the parental origin of the single X chromosome can be varied, can provide insights into neurobiology, keeping in mind important differences between rodents and humans. One such model suggests that several features of the behavioural phenotype may be replicated in the mouse (Lynn and Davies 2007).
Klinefelter syndrome is the most common non-autosomal aneuploidy in live births. It is characterised by the presence of one (or more) X chromosome(s) in boys. The 47,XXY karyotype was demonstrated in 1959 (Jacobs and Strong 1959), whereas the original 1942 clinical report described it as an endocrine disorder characterised by small firm testes, gynaecomastia, hypogonadism and higher than normal concentrations of follicle-stimulating hormone (FSH) (Klinefelter et al. 1942). It is the most common genetic cause of human male infertility.

Epidemiology
Klinefelter syndrome has an estimated prevalence of 1 in 600 live male births (Morris et al. 2002). Many patients with Klinefelter syndrome remain undiagnosed.

Clinical Features
The characteristic phenotype includes microcephaly, tall stature (due to advanced long bone growth from age 2 years) and hypogonadism (requiring testosterone replacement therapy). The full-scale IQ is often in the normal range, but the verbal IQ is commonly low, with occasionally marked speech delay, severe reading and writing difficulties, and impairment of executive functions (Bryant et al. 2012). Boys may appear withdrawn and hypoactive. ASDs may occur.

Genetics and Molecular Biology
In about 80% of cases, Klinefelter syndrome is caused by 47,XXY. In other patients the syndrome may be caused by higher-grade chromosome aneuploidies (48,XXXY, 48,XXYY, 49,XXXXY), mosaicism (46,XY/47,XXY) or structural abnormalities of X chromosomes. Aneuploidy arises through non-disjunction, during meiotic divisions in germ-cell development or less commonly in early embryonic mitotic cell divisions. It appears that the extra X chromosome inhibits fetal brain growth, although the mechanisms are not clear.

Diagnostic Criteria and Testing
A suspected diagnosis can be based on the combination of typical clinical findings, for example, intellectual difficulties in a boy with speech, executive and attentional problems in the context of a (near-) normal full-scale IQ, withdrawn behaviour, tall stature and very small, firm testes. Karyotyping in lymphocytes can confirm the diagnosis. If negative, chromosome analysis can be performed on skin fibroblasts or testicular biopsy samples to confirm mosaicism. Hormonal dosages may also be useful. MRI confirms reduced total brain volume, although specifically reduced frontal and temporal grey matter and spared parieto-occipital grey matter may be found (Bryant et al. 2011) and has been tentatively related with the observed cognitive and behavioural strengths and weaknesses (Giedd et al. 2007).

Animal Models
There are several mouse models. When interpreting findings, it is important to appreciate the existing differences in mechanisms that lead to sexual differentiation of the brain between rodents and humans.

Smith–Magenis syndrome (OMIM#182290) is characterised by dysmorphic features, intellectual disability, distinctive behavioural features, early onset obesity and severe sleep disturbances, mainly related to an inversion in the circadian secretion of melatonin. It is caused by a 17p11.2 deletion. The syndrome was characterised clinically and then cytogenetically in the 1980s by Anne Smith and Ellen Magenis (Smith et al. 1986).

Epidemiology
The prevalence is about 1 in 25 000 live births (Juyal et al. 1996).

Clinical Features
Craniofacial features include brachycephaly, upslanting palpebral fissures, epicanthal folds, wide nasal bridge, midface hypoplasia and prognathism. Short stature, brachydactyly and scoliosis are also common. Congenital heart disease occurs in up to 30% of individuals, including pulmonary or aortic stenosis, valve stenosis or insufficiency, interventricular or interatrial communication, and tetralogy of Fallot.

Most patients have moderate intellectual disability (IQ 40–54), although normal cognition has been reported (Osório et al. 2012). Severity seems to relate to the size of the deletion (Madduri et al. 2006). Children typically have speech delay, with a hoarse voice, and better receptive than expressive skills. Short-term memory, sequential information processing, and visuomotor, attentional and executive abilities are often particularly impaired.

Hypotonia and feeding difficulties are common during infancy, but later behavioural features include propensity towards food, which may lead to obesity in most adolescents (Burns et al. 2010). They also include self-aggression (e.g., biting, head banging, picking at wounds). Children may have frequent temper tantrums and aggressiveness with destructive behaviour (Sloneem et al. 2011). Self-injurious and aggressive behaviours often occur when levels of adult attention are low and lead to increased levels of attention following the
behaviours (Taylor and Oliver 2008). Stereotypies are also common, particularly self-hugging and hand sucking. Anxiety and major depressive disorders have also been reported. ASDs have been reported in a high proportion of patients (Laje et al. 2010), although ascertainment remains an open issue.

Sleep disorders are a hallmark of Smith–Magenis syndrome, particularly the abnormal chronology of the light–dark cycle related to inverted secretion of melatonin (Potocki et al. 2000). Physiologically, secretion of this hormone is triggered by variations in lighting and peaks in the middle of the night. Individuals with Smith–Magenis syndrome have a 12-hour phase shift of this peak, so that they only have residual secretion of melatonin at night. Pharmacological treatment of the sleep disorder may include melatonin in the evening (2–6mg) and beta blockers in the morning (e.g. 10mg/kg acebutolol) (De Leersnyder 2006).

Hyporeflexia is often observed but alterations of nerve conduction velocity are rare. When the deletion involves the PMP22 gene, hereditary neuropathy with a liability to pressure palsy (see Chapter 25) may occur. Reduced response to pain may increase the risk of self-mutilation. About 30% of patients have epilepsy (Goldman et al. 2006).

Genetics and Molecular Biology
Most of the features of Smith–Magenis syndrome are due to haploinsufficiency of the RAI1 (retinoic acid induced 1) gene, whereas the variability and severity of the disorder are modified by other genes in the 17p11.2 region (Elsea and Girirajan 2008). The syndrome can, therefore, be caused by point mutations in RAI1, although it is usually caused by a deletion of about 3.5Mb on chromosome 17p11.2. Other genes that potentially play roles in the phenotype include PMP22, which is involved in hereditary neuropathy with liability to pressure palsy and Charcot–Marie–Tooth-type 1A neuropathy, TNFRSF13B, which may cause IgA deficiency, MYO15A, associated with hearing deficits, and COP9, subunit 3 of the COP9 signallosome, for which a role in melatonin regulation has been suggested (Potocki et al. 2000).

Diagnostic Criteria and Testing
The diagnosis has long relied on demonstration of the 17p11.2 deletion by FISH but this approach has been supplanted by CGH, relative abundance index (RAI), sequencing or whole-exome sequencing. In the case of clinical suspicion without a deletion, RAI1 should be analysed for mutations.

Animal Models
The human chromosome 17p11.2 is syntenic to the 32–34-cM region of murine chromosome 11. The number and order of the genes are highly conserved. A mouse model with a deletion of this region shows phenotypic features that are reminiscent of Smith–Magenis syndrome, such as abnormal circadian activity and being overweight, but normal behaviour, learning and memory (Carmona-Mora et al. 2009). Mice with targeted inactivation of the Rai1 gene have also been studied. The phenotype has been shown to depend on the genomic background, which is, therefore, thought to act as a modifier (Molina et al. 2008).

Sotos syndrome (OMIM# 117550) is an autosomal dominant, developmental, overgrowth syndrome identified since 1964 (Sotos et al. 1964). It is caused by inactivation of the NSD1 gene by mutations or deletions (Kurotaki et al. 2002).

Epidemiology
Sotos syndrome is a common overgrowth condition, although it is apparently less prevalent than Beckwith–Wiedemann syndrome. There have been reports of several hundred individuals affected. The prevalence has been estimated at around 1 in 14,000 live births.

Clinical Features
The craniofacial features appear to be distinctive. They are often fully present at age 6, and include receding hairline, apparent hypertelorism with downsloping palpebral fissures, prominent jaw, malar flushing, anteverted nostrils, mild micrognathia, high-arched palate and large ears (Tatton-Brown et al. 2005). The head circumference is above the 98th centile in infancy, childhood and adulthood in the vast majority of individuals.

Most children show early onset overgrowth, which is particularly marked in the antenatal period and the first year of life (Tatton-Brown et al. 2005), despite feeding difficulties which may be severe in infancy (Cole and Hughes 1994). The length commonly increases more than the weight, with advanced bone age in virtually all individuals. Between age 2 and 6 years, the height is consistently above the 97th centile. Growth tends to normalise at puberty, probably due to epiphyseal fusion, so that adult height is often in the (high) normal range. Large hands and feet are also consistent features.

Learning difficulties are present in almost all patients (Tatton-Brown et al. 2005), although the mean IQ is 76 (de Boer et al. 2004). Most individuals have a delay in expressive verbal language. Attention-impaired, placid behaviour and social inhibition are features of the behavioural phenotype. Most patients show a coordination disorder.

Neonatal hypotonia is common (Cole and Hughes 1994). Congenital heart defects occur in about 20% (Tatton-Brown et al. 2005). Urogenital anomalies, such as renal malformation,
occur in 15% and orthopaedic problems, such as congenital hip dislocation and scoliosis, in 30% of patients.

Genetics and Molecular Biology
Mutations of the NSD1 gene are found in up to 90% of patients, whereas chromosome 5q35 deletions that involve NSD1 cause Sotos syndrome in about a further 10% of patients (Kurotaki et al. 2002). This gene encodes the nuclear receptor SET domain-containing protein-1, which is a histone methyltransferase that plays epigenetic regulatory roles during embryonic development, and perhaps during fetal development and adult brain organisation. It has, therefore, been suggested that Sotos syndrome results from a genome-wide alteration of the DNA methylation of genes that have key roles in cellular morphogenesis and neuronal differentiation (Choufani et al. 2015).

Recently, a homozygous frameshift APC2 gene mutation was demonstrated in two siblings with features of Sotos syndrome (Almuriekhi et al. 2015). The gene product is a downstream partner of NSD1.

Diagnostic Criteria and Testing
Clinical diagnostic criteria were suggested before the molecular basis for the syndrome was identified, based on a thorough assessment of data from 41 typical patients (Cole and Hughes 1994). The criteria are organised into the following four major aspects: overgrowth with advanced bone age, macrocephaly, characteristic facial features and intellectual disability. Currently, as a mutation or deletion can be demonstrated as a cause for NSD1 haploinsufficiency in almost all patients, the diagnosis ultimately relies on genetic testing. In NSD1-negative cases, the possibility of an APC2 gene mutation should be considered.

Animal Models
Despite a high level of homology between human NSD1 and murine Nid1 genes (83% at amino acid level), heterozygous Nid1 knockout mice do not display any of the typical phenotypic features of Sotos syndrome (Rayasam et al. 2003). More recently, chromosome engineering to generate segmental monosomy in mice, leading to a heterozygous 1.5-Mb deletion of 36 genes on mouse chromosome 13, syntenic with 5q35.2–q35.3 in humans, showed surprisingly decreased postnatal growth, in contrast to Sotos syndrome. However, these mice showed impairment in long-term memory retention and dilatation of the pelvicalyceal system, which may in part model the learning difficulties and renal abnormalities observed in patients. An Apc2-deficient mouse model seems to recapitulate some cognitive and facial features of Sotos syndrome (Almuriekhi et al. 2015).

CRI-DU-CHAT SYNDROME
Cri-du-chat syndrome (OMIM#123450) is characterised by craniofacial dysmorphism, severe developmental delay and a high-pitched, cat-like cry (hence the name of the syndrome). It is caused by deletions in the short arm of chromosome 5 (involving at least 5p15.2). It was first described by Lejeune et al. (1963).

Epidemiology
Incidence ranges between 1 in 15 000 (Higurashi et al. 1990) and 1 in 50 000 (Niebuhr 1978) live-born infants.

Clinical Features
Low birthweight, microcephaly and the typical facial features are present at birth. The last includes round face, hypertelorism, epicanthal folds, downward-slanting palpebral fissures, low-set ears, wide nasal bridge, down-turned corners of the mouth and micrognathia. Dermatoglyphics show excess arches on fingertips and transverse flexion creases. The characteristic cat-like cry is probably due to laryngeal and epiglottal anomalies as well as neurological factors (Niebuhr 1978). There may be additional malformations, such as congenital heart defects, brain dysplasia, urogenital malformations and syndactyly.

In the neonatal period, there is marked hypotonia, weak sucking and respiratory problems. Failure to thrive is almost always present, height being less affected than weight. The developmental delay is severe, although a proportion of children eventually walk. Hypotonia is gradually replaced by hypertonia. Verbal development is also slow but almost all children make short sentences by 10 years of age (Cerruti Mainardi 2001). Epilepsy is rare.

Genetics and Molecular Biology
Cri-du-chat syndrome is a contiguous gene syndrome. The 5p deletions can vary in size from involving only band 5p15.2 to affecting the whole short arm of chromosome 5. Numerous repetitive sequences may account for the instability of this region. The deletion occurs on the paternally inherited chromosome in most cases. Most deletions occur anew but about 10% result from unbalanced segregation of translocations or recombination involving a pericentric inversion in one of the parents. Comparison of the observed deletions identified chromosomal regions that were associated with specific clinical features. A region involved in the characteristic cat-like cry is proximal to 5p15.3. A separate region at p15.3 appears to be involved in speech delay. A region of about 2Mb involved in the other manifestations of the syndrome maps to central 5p15.2 (Overhauser et al. 1994).

Among the possibly relevant genes in these regions, SEMAF, encoding semaphorin F, might be implicated in some
features through its role in guiding axons or migrating neuronal precursors during cortical development. CTNNND2, which is also located in 5p15.2, encodes δ-catenin, which is involved in cell motility and expressed early in neuronal development (Medina et al. 2000). Another candidate gene, encoding the telomerase reverse transcriptase, maps to 5p15.33.

**Diagnostic Criteria and Testing**

The diagnosis is made by demonstration of the 5p deletion, commonly by CGH. It has been suggested by some that the characteristic facial features are pathognomonic (Corcueraflores et al. 2016). However, recognition of the syndrome based on facial features has been shown to be inaccurate, particularly with respect to other dysmorphic syndromes, such as fragile X syndrome, Cornelia de Lange syndrome, Williams syndrome, Prader–Willi syndrome, Sotos syndrome, 22q11.2 deletion syndrome or Noonan syndrome, perhaps because of the greater variation in facial appearance with age (Boehringer et al. 2006).

**Animal Models**

Mouse models with knockdown of Ctnnd2, resulting in overall loss of δ-catenin or selective loss of δ-catenin in pyramidal neurons, has yielded early promising results for understanding of the role of δ-catenin in synaptic architecture and neural circuit formation (Yuan et al. 2015).

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**KABUKI SYNDROME**

Kabuki syndrome (OMIM#147920) is an example of a condition related to mutations in the methylation enzymes involved in epigenetic marking, for which research in animal models suggested possible treatment with histone deacetylase inhibitors, such as sodium valproate or ketogenic diet. It is recognizable clinically based on its distinctive facial features, postnatal growth retardation, intellectual disability, skeletal abnormalities and unusual dermatoglyphic patterns. It was first identified in 1969 in a child with cognitive impairment by the Japanese geneticist Norio Niikawa who noted that the unusual facial features were reminiscent of the make-up that is typical in traditional Kabuki theatre. The first reports underlined this aspect, referring to the condition as Kabuki make-up syndrome (Niikawa et al. 1981), though the term ‘make-up’ is no longer used because it is considered potentially derogatory.

**Epidemiology**

Initially, Kabuki syndrome was believed to be specific to the Japanese population, although the condition has now been reported in a wide variety of ethnic types. Prevalence estimates in Japan are about 1 in 30 000 (Niikawa et al. 1988).

**Clinical Features**

Patients often have long palpebral fissures with eversion of the lower eyelid, arched eyebrows with sparseness in the lateral part, prominent ears and depressed nasal tip. The facial features tend to become more pronounced as the child grows. Skeletal anomalies include spinal deformity and brachydactyly of the fifth digit. Dermatoglyphic abnormalities are typical. Most individuals have postnatal growth deficiency and mild-to-moderate intellectual impairment.

**Genetics and Pathophysiology**

Kabuki syndrome is caused by heterozygous mutations in KMT2D on chromosome 12q13 (Ng et al. 2010). A wide spectrum of new, mostly private mutations can be found in up to 80% of individuals with a clinical diagnosis (Banka et al. 2012). Familial occurrence has also been reported, with an autosomal dominant inheritance pattern (Bogershausen and Wollnik 2013). Most of these mutations result in haploinsufficiency. The gene product, a histone H3 lysine 4 (H3 K4)-specific methyltransferase, is involved in making chromatin marks that are crucial for the inheritance of active transcriptional states (Muramoto et al. 2010). In patients in whom no KMT2D mutation is found, mutations are occasionally identified in KDM6A on chromosome Xp11.3 (Lederer et al. 2012; Miyake et al. 2013), which also encodes a histone modifier that interacts with KMT2D (Schuettengruber et al. 2007).

**Diagnostic Criteria and Testing**

Clinical diagnostic criteria were suggested by Adam and Hudgins (2004), based on the presence of facial features, skeletal abnormalities, dermatoglyphic features, intellectual disability and postnatal growth deficiency. As for the other conditions in this chapter, CGH (and possibly whole-exome sequencing) plays a prominent role in the diagnostic approach.

**Animal Models**

A mouse model was engineered with a heterozygous deletion in the Kmt2d gene (Bjornsson et al. 2014). The animals show an impaired methyltransferase function and reduced histone acetylation. However, administration of a histone deacetylase inhibitor to young or adult mice was demonstrated to reverse both structural and functional deficits (Bjornsson et al. 2014). These promising results suggest that patients with Kabuki syndrome could be treated by agents modulating epigenetic processes.
REFERENCES


PART III

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Osseous Malformations of the Skull and Craniovertebral Junction

Richard Hayward and Dominic Thompson

Osseous Malformations of the Skull

Craniosynostosis
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- Sagittal Synostosis
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- Lambdoid Synostosis – and Posterior Positional Moulding
  - Lambdoid Synostosis Versus Posterior Positional Moulding
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- Apert Syndrome
- Pfeiffer Syndrome
- Cloverleaf Skull (Kleeblattschädel) Deformity
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- Cranio-Fronto-Nasal Dysplasia
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Osseous Malformations of the Skull
and Craniovertebral Junction

Richard Hayward and Dominic Thompson

This chapter reviews the abnormalities of the osseous skull and craniofacial syndromes (RH) and the disorders of the cervicovertebral junction (DT), as well as their consequences on the underlying central nervous system and associated malformations.

**Table 6.1** Classification of causes of craniosynostosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Idiopathic: No genetic cause either known or suspected</td>
</tr>
<tr>
<td></td>
<td>Genetic cause known or suspected: Gene mutation(^a)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>Metabolic: Vitamin D deficient rickets, Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Disorders of bone metabolism: Cranio-meta/diaphyseal dysplasia, Osteopetrosis</td>
</tr>
<tr>
<td></td>
<td>Storage disorders: Hurler syndrome, Morquio syndrome</td>
</tr>
<tr>
<td></td>
<td>Drug induced: Metopic synostosis, as part of the fetal valproate syndrome</td>
</tr>
<tr>
<td></td>
<td>Physical distortion: Post-CSF shunting positional scaphocephaly</td>
</tr>
</tbody>
</table>

\(^a\)The majority of single suture synostosis fall into this category – in particular those affecting the sagittal and metopic sutures.

\(^b\)This includes not only the syndromes once described eponymously (Crouzon, Apert etc.) but also many previously labelled as non-syndromic that have now had their underlying gene mutation mapped.

\(^c\)The metopic suture appears to be the most vulnerable when craniosynostosis forms part of a chromosomal abnormality – a deletion of part of the short arm of 7, for example.

CSF, cerebrospinal fluid.

**CRANIOSYNOSTOSIS**

Craniosynostosis is defined here as the premature closure of one or more of the skull vault sutures. While advances in molecular genetics have revolutionised our understanding of the various syndromes that may include craniosynostosis, and improved imaging techniques have provided new information about not only the calvarial sutures but also changes affecting the skull base and facial skeletons, the initial diagnosis (or more accurately the initial suspicion) of craniosynostosis still depends primarily on the patient’s – usually a child’s – appearance.

The aim of this chapter is to provide for the paediatric neurologist a broad overview of this complex subject. For convenience craniosynostosis affecting a single vault suture (sometimes referred to as ‘simple’ synostosis) will be dealt with separately from the various complex/syndromic forms in which premature closure of several – sometimes all – of the skull sutures is usual although overlap between the two groups is not uncommon. Johnson and Wilkie have provided a useful overview from a craniofacial surgeon and geneticist’s perspective (Johnson and Wilkie 2011).

The various causes of craniosynostosis (or conditions with which it may be associated) can be broadly classified as shown in Table 6.1.

**SINGLE SUTURE SYNOSTOSIS**

The direct consequences of premature fusion of a single skull vault suture are for the most part cosmetic – the result of a usually characteristic alteration in head shape. Effects on the facial skeleton, if any, are modest and severe functional consequences affecting vision, breathing and feeding, for example, are rare. This is in marked contrast to the complex/syndromic forms of craniosynostosis in which such issues are common.
Aetiology

While the majority of cases of single suture synostosis arise as isolated events the possible genetic implications of the diagnosis should not be overlooked particularly for unicoronal synostosis (Moloney et al. 1997) (see Unicoronal [and Fronto-Sphenoidal] Synostosis). Whereas no common candidate genes are presently known for isolated sagittal and metopic synostosis, it is essential that all children with unicoronal synostosis are referred for evaluation by a geneticist (Johnson and Wilkie 2011).

Pathogenesis of Single Suture Synostosis

The first ‘modern’ explanation for the head shape that results from single suture synostosis is attributed to Virchow (quoted by Alden et al. 1999) who described restricted growth at 90° to the affected suture and exaggerated growth parallel to it. Add a palpable and sometimes visible ridge along the suture itself and, though this analysis can be considered simplistic in the light of more contemporary studies of suture biology, it still serves as a convenient model for discussions with parents.

Modern interest (Cousseens et al. 2007) in the biology of premature suture closure was initiated by Moss who introduced the concept of the Functional matrix in which both morphogenetic and functional forces combine to produce the final anatomical result (Moss 1975). Since then there has been great progress in the actions of various genes [e.g. TCF12 (Sharma et al. 2013) and ERF (Twigg et al. 2013)] on the biology of osteogenesis in general and suture formation in particular (see The Molecular Genetics of Syndromic Craniosynostosis).

Diagnosis of Single Suture Synostosis

The diagnosis of single suture craniosynostosis is primarily one of pattern recognition. The various types produce head shapes so characteristic that confirmation by some form of imaging is rarely required by those with craniofacial experience. For those without this advantage the following imaging modalities can be useful.

1. Plain X-rays can be diagnostic for sagittal, unicoronal and lambdoid synostosis. The metopic suture closes so early in life (during the first year) that its absence on an X-ray is no proof that it might have closed early. The hypotelorism and vertical medial orbital walls associated with metopic synostosis are however recognisable on an antero-posterior skull X-ray.

2. Computerised Tomography (CT) can be diagnostic by revealing not only the skull shape (visible on clinical examination) but by demonstrating the absent suture – particularly on three-dimensional reconstructions. They will also reveal any associated cerebral abnormalities.

3. Magnetic resonance imaging (MRI) does not show bone with sufficient resolution to have a role in the routine diagnosis of craniosynostosis. It is only indicated when neurological/developmental concerns suggest a possible brain abnormality.

Natural History of Single Suture Synostosis

The natural history of most forms of single suture synostosis is that the abnormality of head shape for which they are responsible commences well before birth – as shown by their occasional presence in the preterm infant. The change in head shape may become more obvious over the first year of life but major changes are unusual. The parents of an affected child can, therefore, be told that without intervention their child’s head shape is likely to remain much as it is when first seen.

Implications of Single Suture Synostosis

Parents need to be warned that single suture synostosis does carry implications for the affected child’s neurodevelopmental progress (Starr et al. 2012). Although the majority of affected children are likely to be unaffected a significant proportion will manifest a degree of delay. This is most frequent when there is an associated chromosomal abnormality (seen most in children with metopic synostosis) or gene mutation (e.g. unicoronal synostosis due to Muenke or FGFR3-associated synostosis). Fetal valproate syndrome also combines developmental delay/learning difficulties with metopic synostosis (Lajeunie et al. 2001).

The cause of such cognitive impairment in most cases, however, remains unknown. Although it has sometimes been attributed to occult raised intracranial pressure (ICP) the evidence remains weak (see Functional Complications of Syndromic Craniosynostosis section for a discussion of raised of ICP in children with complex/syndromic forms of craniosynostosis). Reviewing single suture synostosis in general, Kapp-Simon et al. (2007) stated that, ‘Surgical intervention on morphologic [appearance] grounds remains the only absolute indication’. And single Suture fusion may serve as an indicator of neurodevelopmental concern. In other words, the relationship between single suture premature fusion (such as the metopic) and neurocognitive problems may not be causal. Finally, Hankinson et al. (2010) concluded that, ‘Taken as a whole, the current literature suggests that cognitive impairment in children with SSC [single suture craniosynostosis] occurs despite early surgical intervention’.

Nevertheless, there remains a body of opinion amongst those involved in the management of children with single suture synostosis that a certain percentage will, if left untreated, develop otherwise avoidable cognitive/developmental problems (Eley et al. 2012).

In brief, however, although raised ICP as confirmed by the discovery of papilloedema can occasionally occur in children with single suture synostosis (particularly in older children with sagittal synostosis regardless of whether or not they have had surgery), the premature closure of a single skull vault suture remains primarily a cosmetic issue when the benefits and risks of intervention are discussed with parents.
Management of Single Suture Synostosis

Decisions concerning treatment for a primarily cosmetic condition in a child usually too young to have an input to the decision-making process involves a delicate discussion between parents and specialist in which they (the parents) have to weigh the severity with which they view the abnormality of their child’s appearance (and its possible consequences – e.g. teasing at school) against the benefits (in terms of appearance change) and the risks (to the brain from some unexpected complication of surgery such as haemorrhage or infection) never absent from what is never a minor cranial operation.

The various surgical interventions (and their timing) currently employed in the management of each single suture synostosis are here briefly described. For a more detailed summary, see the review by Garza and Khosla (2012).

SAGITTAL SYNOSTOSIS

Premature closure of the sagittal suture is the most frequent form of craniosynostosis and leads to a characteristic scaphocephalic (boat-shaped) deformity of the skull. A prevalence of approximately 1 in 5000 children has been estimated and the condition is more frequently seen in boys. Six per cent of cases are familial with transmission following an autosomal dominant pattern with a penetrance of 38% (Lajeunie et al. 1996).

The affected skull has an increased antero-posterior diameter, but its bi-parietal diameter is reduced (Fig. 6.1) and a bony ridge can often be both seen and felt along the line of the fused suture (victims of teasing may be called ‘peanut head’). The synostotic process does not always involve the entire suture and even when it does the severity with which the child’s head shape is affected is very variable, with a mild prominence of the forehead at one end of the spectrum to gross elongation (frontal and occipital bossing) plus narrowing (particularly in the pterional regions) at the other.

The variety of surgical treatments presently employed for the correction of sagittal synostosis (for those children whose parents have opted for intervention) suggests either that all are equally effective – or equally non-effective. The operations vary in scale from removal of the fused suture (suturectomy) combined with internal springs (de Jong et al. 2013) or external (helmet/orthosis) manoeuvres (Proctor 2012) designed to induce a more round shape (all of which need to be performed before six months of age to be most effective) to increasingly major forms of skull reconstruction for which there are no age limits.

UNICORONAL (AND FRONTO-SPHENOIDAL) SYNOSTOSIS

Craniosynostosis of a single coronal suture produces a characteristic asymmetry of the forehead: frontal plagiocephaly. The supra-orbital ridge on the affected side is recessed as is the forehead above while the temporal region is unusually prominent. On the contralateral side the frontal region is often bossed, accentuating the asymmetry and the nose is set an angle, its root ‘pointing’ towards the side of the affected suture. The net result is to give the face a characteristic ‘scoliosis’ or curve convex to the affected side. The anterior skull base is also curved – but concave to the affected side (Fig. 6.2).

The elevation of the lateral wing of the sphenoid bone on the affected side is responsible for the characteristic ‘harlequin eye’ appearance on an antero-posterior skull X-ray.

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**Figure 6.1** Three-dimensional CT scans showing the typical scaphocephalic head shape caused by sagittal synostosis.

**Figure 6.2** Three-dimensional CT scan showing the typical deformity caused by unicoronal synostosis.
deformation of the orbit results in a subtle malposition of
the extra-ocular muscle attachments that may in turn cause
a complex abnormality of eye movement and a secondary
compensatory head tilt (Gosain et al. 1996). All children with
unicoronal synostosis should, therefore, be referred to a
paediatric ophthalmologist.

Although the cause of uniconoral synostosis is in many cases
unknown it can result from a variety of genetically mediated
disorders. Most prominent amongst these is the Muenke
(or FGFR3-associated synostosis) (Muenke et al. 1997).
Saethre–Chotzen syndrome (Reardon and Winter 1994) and
cranio-frontonasal dysplasia (Cohen 1979) may also involve
premature closure of a single coronal suture but their other
features are usually sufficiently characteristic to suggest the
diagnosis.

It is unusual for children with isolated non-genetically
mediated uniconoral synostosis to have impaired neurocogni-
tive development. Such problems are, however, well described
for children with the FGFR3 mutation (Wilkie et al. 2010;
Johnson and Wilkie 2011).

Treatment of uniconoral synostosis consists of a fronto-
orbital reconstruction, a procedure that for the most satis-
factory result may require attention to both the affected and
contralateral sides. Although a gratifying immediate result
can usually be obtained with abolition of the previous frontal
plagiocephaly, there is over the years that follow a tendency
for some element of the previous deformity to reassert itself.
This is seen at its greatest extent in those children harbouring
the FGFR3 mutation (Wilkie et al. 2010).

A rare cause of unilateral frontal flattening that can be
confused with uniconoral synostosis is premature closure of
the fronto-sphenoid suture. It can be recognised clinically by
the degree of frontal plagiocephaly being particularly severe
and the nose angled in the opposite direction – its root away
from the affected side. Its treatment, however, is the same as
for uniconoral synostosis. CT reveals a normal coronal suture
with an absent fronto-sphenoidal suture.

METOPIC SYNOSTOSIS

The metopic suture is the first of the major calvarial sutures
to close, a process often completed by the end of the first
year. Mild vertical ridging along the line of the suture is not
uncommon and should be considered a normal variation
for which investigation in the absence of other issues is not
required. Premature closure of the metopic suture however
produces a characteristic triangular (when viewed from above)
deformity of the anterior skull (trigonocephaly). There is a
keel-like prominence running vertically down the centre of
the forehead while the supra-orbital ridges and the frontal
bones above them are flattened on each side (Fig. 6.3). The
anterior cranial vault is narrow with approximation of the
orbits – hypotelorism – and prominent epicanthic folds.

In a large study of metopic craniosynostosis, Lajeunie et al.
(1998) estimated a prevalence of 1 in 15 000 with 5.6% of
cases being familial. As with sagittal synostosis there is a
male preponderance of approximately 3:1. Maternal expo-
sure to sodium valproate is also a risk factor in the devel-
oment of metopic craniosynostosis (Lajeunie et al. 2001), but
the affected child has (in addition to learning difficulties
and other components of the syndrome) hyper- rather than
hypo-telorism.

Even in the absence of an associated syndromic or chro-
mosomal abnormality children with metopic synostosis may
grow up with learning difficulties (Bottero et al. 1998). The
effect of the orbital deformity upon their ophthalmic func-
tion include a higher incidence of both refractive errors and
astigmatism than would otherwise be expected – and no
relationship to age at surgery (Macintosh et al. 2011).

Treatment involves, as for uniconoral synostosis, a fronto-
orbital reconstruction in which the central keel is removed
together with the recessed superior orbital margins and the
flattened frontal bones. These pieces are reconstructed into a
more regular contour and replaced. As with uniconoral syn-
ostosis some reversion is not uncommon with a return of a
(usually minor) degree of lateral frontal flattening.

LAMBDOID SYNOSTOSIS

AND POSTERIOR POSITIONAL MOULDING

Isolated unilambdoid synostosis is rare, accounting for only
2.3% of Shillito and Matsons series of 519 patients (Shillito
and Matson 1968). Its importance lies in its differentiation
from acquired positional posterior flattening (plagiocephaly).
The affected child is born with the posterior parietal/occipital
area on one side of the head flattened and restricted
in volume while the contralateral frontal area may be more
prominent than the ipsilateral (Matushita et al. 2014). As with
the other isolated single suture synostoses this deformity shows
little spontaneous tendency either to progress or to worsen.
Given its posterior (eventually hidden by hair) location and
Lambdoid Synostosis Versus Posterior Positional Moulding

Posterior flattening of the skull (uni- or bilateral) can also occur as a result of skull moulding, a condition seen with greatly increased frequency since the advent of the ‘Back to sleep’ campaign to reduce the risk of cot death/sudden infant death syndrome (SIDS) (Kane et al. 1996). The risk factors for acquired positional moulding include preterm birth, a head with some intra-uterine flattening at birth, a tendency to lie with the head turned preferentially in one direction (torticollis – with or without a sternomastoid ‘tumour’), a firm mattress to sleep on, no pillow and finally a being ‘good baby’ – one who sleeps through the night with little change in position. With these factors at work an infant whose head might have been perfectly round at birth can by the age of 6 weeks or so have developed marked flattening of one side of the back of the head. Viewed from above it is as if that region has been pushed forward, taking with it the ipsilateral ear (moving it closer to the eye on the affected side [Fig. 6.4]) and producing a degree of ipsilateral frontal prominence (Huang et al. 1998). For the next 6 months or so there a tendency for the deformity to become more pronounced until with the child’s greater independence of movement he or she no longer lies through-out the night in the same position and the skull has acquired sufficient rigidity to resist further pressure-inflicted change. From then on there is a tendency for further skull growth to bring with it a degree of ‘correction’ of the head shape although when marked to begin with this, this is never complete.

Posterior positional moulding can be associated with motor delay but the causal connection is due to the less active child being more liable to develop the flattening – not the other way round. Given the history and the typical head shape (Huang et al. 1998), it is usually possible to differentiate posterior positional moulding from lambdoid synostosis on clinical grounds alone; but when in doubt a skull X-ray will show whether that suture is open or not.

The mainstays of management are awareness and prevention. Once the condition has been recognised for what it is, however, treatment consists of repositioning during sleeping and feeding, physiotherapy as required for torticollis, and moulding mattresses. Head re-shaping orthoses (moulding helmets) may have a role in both limiting the degree of deformity and restoring a more regular growth pattern particularly when instituted below the age of 6 months (Collett 2014; van Wijk et al. 2014). There is as little if any place for the surgical correction of the posterior deformity that results from positional moulding as there is for that due to lambdoid synostosis.

**CRANIOSYNOSTOSIS AND CRANIOFACIAL SYNDROMES**

The craniofacial syndromes are a heterogeneous group of rare conditions in which craniosynostosis occurs alongside various manifestations of disordered craniofacial development (Rice 2008) as well as other skeletal abnormalities that can affect, in particular, the hands and feet (Britto et al. 2001a; Panthaki and Armstrong 2003).

The conditions seen most frequently are the eponymous syndromes of Crouzon, Apert, Pfeiffer, Saethre–Chotzen, Muenke (FGFR3-associated synostosis) and crano-fronto-nasal dysplasia. Less commonly encountered are Carpenter, Antley–Bixler (Antley and Bixler 1975; Bradley et al. 2003), Jackson–Weiss (Jackson et al. 1976) and Boston-type syndromes.

The aim of management is to ensure that affected children realise their full developmental potential. Although a major component of treatment is surgical there is now recognition of the needs of the child as a whole. The centres best placed to achieve this are those that can field the multidisciplinary team that, in addition to its neuro-, plastics and maxilla-facial surgeons, includes specialists in otorhinolaryngology and audiology, genetics, paediatrics, neurology, psychology, orthodontics, respiratory medicine, speech therapy, ophthalmology and, of course, paediatrics (Hayward and Jones 2004).

**CROZON SYNDROME**

Crouzon syndrome (Cohen and Kreiborg 1992), like the majority of craniofacial syndromes, is transmitted as an autosomal dominant condition although it occurs with near equal frequency as a new mutation. As in Apert syndrome, its occurrence is associated with increased paternal age (Glaser et al. 2000).

Typical clinical features include a retruded maxilla that leaves the lower teeth projecting anterior to the upper teeth (class III malocclusion), a ‘beaky’ nose, a recessed frontal region (brachycephaly) due to bicoronal synostosis. The conditions seen most frequently are the eponymous syndromes of Crouzon, Apert, Pfeiffer, Saethre–Chotzen, Muenke (FGFR3-associated synostosis) and crano-fronto-nasal dysplasia. Less commonly encountered are Carpenter, Antley–Bixler (Antley and Bixler 1975; Bradley et al. 2003), Jackson–Weiss (Jackson et al. 1976) and Boston-type syndromes.
prominent eyes (exorbitism) due to the combined recession of the infra- and supra-orbital regions (Fig. 6.5).

Its expression is highly variable, ranging from severe exorbitism with midface retrusion and airway obstruction at one extreme to a mild prominence of the eyes at the other. A catch for the unwary is that suture fusions need not be present at birth but may develop during the first 2 years of life (Reddy et al. 1990; Connolly et al. 2004). Extracranial manifestations (Anderson 1997) seen in severe cases include vertebral fusion (most commonly cervical) (Anderson et al. 1997a, 1998a) and ankylosis affecting particularly the elbows (Anderson et al. 1998a).

A genetically distinct type of Crouzon syndrome is associated with rugated thickened skin and hyperpigmentation that affects particularly the flexure creases – acanthosis nigricans (Wilkes et al. 1996).

Intelligence may be normal in Crouzon syndrome but the more severe the phenotype the more likely the child is to have developmental and learning difficulties. Marked intellectual disability was present in 3% of Kreiborg’s series (Kreiborg 1981).

APERT SYNDROME

The child with Apert syndrome has a head that is tall and shortened from front to back (turri-brachycephaly), midfacial (maxillary) retrusion, proptosis, a downward slant to the palpebral fissures and hypertelorism (Lajeunie et al. 1999) (Fig. 6.6a). The essential clinical feature however is a complex fusion (syndactyly) of the fingers and toes (Anderson et al. 1997d, 1999; Cohen and Kreiborg 1995b) that may require multiple surgical procedures before functional effectiveness is achieved (Guero et al. 2004) (Fig. 6.6b). Visceral (Cohen and Kreiborg 1993) and cutaneous (Cohen and Kreiborg 1995a) abnormalities can also occur. Palatal abnormalities (Kreiborg and Cohen 1992) ranging in severity from frank clefts to a bifid uvula are common and occur with a frequency of up to 75% (Peterson and Pruzansky 1974; Slaney et al. 1996). Cervical vertebral fusions that may be progressive occur in over half of affected children although it is unusual for them to become clinically significant (Thompson et al. 1996).

Developmental and learning difficulties are the norm in Apert syndrome although a combination of developmental assessment tools designed for children without Apert syndrome and low societal expectations may overestimate their severity (Shipster et al. 2002). While a small percentage of children may complete secondary education (and usually only with assistance in the classroom), many drop out of mainstream education during their primary school years while a small percentage are too affected for the mainstream education system at anything above kindergarten level (Patton et al. 1988; Renier et al. 1996).

PFEIFFER SYNDROME

Although described separately for historical reasons, the genetic overlap between Pfeiffer and Crouzon syndromes is such that they are now often considered together as ‘Crouzon–Pfeiffer syndrome’.

The ‘traditional’ Pfeiffer syndrome is an autosomal dominant condition characterised by suture fusions that range from bicoronal synostosis alone to pan-synostosis (with or without the cloverleaf skull deformity – see below) (Winter 1994). Affected patients also have digital abnormalities (Panthaki and Armstrong 2003) that include curved and shortened thumbs and great toes (Anderson et al. 1998b) and, less commonly, digital fusions [although to a lesser degree than in Apert syndrome (Panthaki and Armstrong 2003)].

Cohen (1993) divided children with Pfeiffer syndrome into three types based on their clinical severity. Type 1, those least affected, may display little more than bicoronal synostosis and midface retrusion (in addition to their digital
abnormalities). Their neurocognitive development may be unaffected, particularly if early complications have been aggressively treated (Kohan et al. 2009) (Fig. 6.7).

In Types 2 and 3 Pfeiffer syndrome, the degree of midface and frontal retrusion is severe enough to obstruct the upper airway and cause eye protrusion sufficient to threaten the corneas. The shortening of the skull base and crowding of the posterior fossa due to the bi-lambdoid component of their pan-synostosis produces an increased risk of hydrocephalus. Ankylosis (bony and soft tissue) of the elbows (Anderson et al. 1998a) and knees is common as are fusions of the cervical vertebrae (Anderson et al. 1996b).

The difference between Types 2 and 3 is that Type 2 has the cloverleaf pattern of skull deformity (see below).

Neurocognitive development in Types 2 and 3 Pfeiffer syndrome is usually delayed although with active intervention aimed at improving the airway and reducing raised ICP the outlook is not as dire as was once assumed (Robin et al. 1998). CLOVERLEAF SKULL (KLEEBLATTSCHÄDEL) DEFORMITY

The Kleeblattschädel anomaly, or cloverleaf skull, is the descriptive term given to a particularly severe form of synostosis-associated cranial deformity (Zuleta and Basauri 1984) – and one that poses a particular challenge for the craniofacial surgeon (Thompson et al. 1995b; Zuccaro et al. 1996). Although it usually occurs as a manifestation of Pfeiffer syndrome (Type 2) it can occasionally complicate Apert and Crouzon syndromes (Fig. 6.8).

Its cause is a particular combination of suture fusions and an ICP that is raised from hydrocephalus. The sagittal and squamo-parietal sutures are open but in addition to bicoronal synostosis, a bony constriction band runs posteriorly from the pterions to the lambdoids. With the addition of hydrocephalus the infant’s skull expands upwards (above) and laterally (below) this constriction band to produce the characteristic trefoil (cloverleaf) shape (Cohen 1972, 1993; Eaton et al. 1975; Kroczek et al. 1986).

SAETHRE–CHOTZEN SYNDROME

Saethre in 1931 and Chotzen in 1932 described an autosomal dominant condition that combines with great variability (Reardon and Winter 1994) coronal synostosis (uni- or bilateral) and digital abnormalities that include short digits and partial syndactyly (Anderson et al. 1996a), low frontal hairline, a prominent nose and ptosis, and more rarely fusions of the cervical spine (Anderson et al. 1997b) (Fig. 6.9). Complications such as exorbitism and airway obstruction are uncommon. Raised ICP is rarely of functional significance (de Jong et al. 2010) and the neurocognitive outcome may be only modestly affected if at all (Reardon and Winter 1994).

MUENKE SYNDROME

(MUENKE SYNDROME

(FGFR3-ASSOCIATED SYNOSTOSIS)

This condition, one of the less severe of the craniosynostosis-associated syndromes, is of interest because rather than being first described on the basis of the appearance of those affected it was ‘discovered’ during the explosion of knowledge about the genetic basis of the craniofacial syndromes that occurred during the 1990s (Muenke et al. 1997).

It has multiple manifestations (Reardon et al. 1997) but the synostosis typically affects one or both coronal sutures (Moloney et al. 1997). It is now appreciated that many patients previously diagnosed as isolated unicoronal craniosynostosis carry the FGFR3 mutation (Lajeunie et al. 1995a). Those with bicoronal synostosis typically have a broad and shallow supra-orbital region with a protruding upper forehead (Fig. 6.12a, b). Complications such as raised ICP and airway obstruction are uncommon but although a child’s development may be unaffected, a degree of learning difficulty is well described (Muenke et al. 1997).
CRANIO-FRONTO-NASAL DYSPLASIA

In this X-linked (Pulleyn et al. 1999) syndrome, bicornal synostosis (usually asymmetrical in its effect) is associated with hypertelorism, wiry (‘unruly’) hair, a prominent gap between the central incisors, a bifid nose (Cohen 1979; Pruzansky et al. 1982; Saavedra et al. 1996) and sometimes abnormalities of the optic discs (Lees et al. 1998). Development is usually unaffected and treatment is indicated on predominantly cosmetic grounds (Kawamoto et al. 2007).

CARPENTER SYNDROME

This very rare condition (Carpenter 1909) is mentioned here for completeness because it has an autosomal recessive pattern of inheritance. Also known as acrocephalopolysyndactyly because of the extra digits that form part of the clinical picture, the cranial deformity is due to various combinations of craniosynostosis (Eaton et al. 1974; Gershoni-Baruch 1990).

The Molecular Genetics of Syndromic Craniosynostosis

It was hoped that when the genetic basis of many of the craniofacial syndromes was discovered in the 1990s it would allow their classification to move from the eponymous nomenclature that had been in use for so many years. Unfortunately, as the genetic ‘overlap’ between Crouzon and Pfeiffer syndromes demonstrates, the situation proved to be more complex: a single mutation capable of causing both Pfeiffer and Crouzon syndrome and mutations on either of two chromosomes responsible for Pfeiffer syndrome (Rutland et al. 1995; Schell et al. 1995; Britto et al. 2001c). It is for this reason that some specialists now prefer the designation ‘Crouzon–Pfeiffer syndrome’ to two separate entities – which, from a clinical management perspective, makes little difference to established practice.

With the exception of Carpenter syndrome (autosomal recessive [Jenkins et al. 2007]) and cranio-fronto-nasal dysplasia (X-linked [Pulleyn et al. 1999]) the craniosynostosis-associated syndromes have an autosomal dominant pattern of transmission. (For a summary linking the clinical features...
of syndromic craniosynostosis to their underlying genetic abnormalities see the review by Rice (2008)).

The realisation that many of the craniofacial syndromes were monogenetic (due to a single gene mutations) combined with investigation of families with several affected members led, in the 1990s, to an intense examination of the fibroblast growth factor group of tyrosine kinase receptors (FGFRs I–III) as candidate genes. These receptors are well preserved across a range of species and are involved (amongst many other activities) in cranial and limb development (Johnson and Williams 1993; Britto et al. 2001b; Robbin et al. 2011). It is now known that a particular position within each FGFR protein is strongly linked to craniosynostosis as mutations there in FGFR 1, 2 and 3 cause respectively Pfeiffer, Apert and Muenke syndromes (Bellus et al. 1996).

More recent genetic discoveries have further reduced the number of cases of craniosynostosis that were once labelled as ‘non-syndromic’. These include mutations involving the TCF12 and ERF genes.

Mutations of TCF12 have been reported in 32% and 10% of children with ‘non-syndromic’ bi- and unicoronal synostosis respectively in whom Muenke, FGFR2 and Saethre–Chotzen mutations had been excluded. The gene is located on chromosome 15, acts synergistically with TWIST1 through ‘loss of function’ and appears to be necessary for the production of a functioning coronal suture (Sharma et al. 2013).

Mutations of ERF are less common than those of TCF12, found in only 1–2% of 402 cases of craniosynostosis operated on by the Oxford craniofacial unit (Twigg et al. 2013). They also act by loss of function to cause complex multi-suture fusions that when associated with facial abnormalities may resemble Crouzon syndrome (there is a ‘pathway-based phenotypic link with FGFR2’ [Twigg et al. 2013]). The sagittal is the most likely to be involved when only one suture is prematurely fused (Twigg et al. 2013). Although confirmation of a particular mutation may not affect a child’s immediate management, it does allow a more informed developmental prognosis and the likely need for subsequent operations to be explained to parents (Wilkie et al. 2010). Knowledge of the responsible mutation also has important implications for genetic counselling. Parents who have already had an affected child may also wish to avail themselves of the opportunity not only for prenatal ultrasound examination of the foetus (Gorincour et al. 2005; Chitty and Lau 2011; Khalil et al. 2011; Shaw et al. 2011) but also for pre-implantation diagnosis when considering further pregnancies (Abou-Sleiman et al. 2002; Harper et al. 2002).

**FUNCTIONAL COMPLICATIONS OF SYNDROMIC CRANIOSYNOSTOSIS**

**Raised Intracranial Pressure**

Raised ICP is a well recognised complication of syndromic craniosynostosis (Renier et al. 1982; Thompson et al. 1995a). Its incidence is strongly related to the severity of the phenotype making it unusual in Muenke and Saethre–Chotzen syndrome and near inevitable in Pfeiffer Type 2 (cloverleaf skull deformity).

Raised ICP can, as a consequence of unrelieved papilloedema, be responsible for a progressive deterioration in vision leading eventually to blindness (Stavrou et al. 1997; Liasis et al. 2011). Whether it can (in the absence of hydrocephalus) affect cognitive development is more assumed than proven. Renier et al. (1996) and others have proposed such a connection but it is difficult to untangle the effects of raised ICP alone from such other manifestations of the affected child’s phenotype as the direct brain effects of the disordered gene or chromosome (Wilkie et al. 2010), hydrocephalus, chronic airway obstruction, feeding difficulties and ‘failure to thrive’, the developmental consequences of impaired vision and/or hearing coupled with low societal and family expectations (including teasing) – not to mention any unintended side effects of earlier cranial surgery (Naumann et al. 2012).

**THE DIAGNOSIS OF RAISED INTRACRANIAL PRESSURE**

Clinical. Bulging of still open fontanelles, stretched sutures and cranietomy defects; and in the older child headache and vomiting although these are of very low sensitivity and specificity.
Radiological. A generalised copper-beaten appearance on skull radiographs in the presence of multiple suture fusions (Tuite et al. 1996b), progressive ventriculomegaly and effacement of cortical sulci on MRI and/or CT (Collmann et al. 2005).

Ophthalmological. Papilloedema (Tuite et al. 1996a) with or without abnormal electro-diagnostic studies and a fall in visual acuity (Liasis et al. 2003, 2006; Thompson et al. 2006).

Invasive ICP monitoring. Transcranial parenchymal pressure monitoring allows ICP to be measured (Renier et al. 1982; Thompson et al. 1995a). However, it is important to recognise that the figures most often used to interpret the results of ICP monitoring in childhood (normal, <10mmHg; borderline, 11–15mmHg) and raised, >15mmHg) are ‘best guesses’ based on a variety of assumptions (parents of healthy children being understandably reluctant to submit them to an invasive procedure for essentially academic interest).

It is important to remember that although ICP may be normal when a child first presents, the dynamic nature of the syndromic craniosynostosis process means that surveillance (which in our unit includes regular ophthalmic assessments) should continue until a child is at least 8 years old; our experience being that it is unusual for it to develop – or recur – after that age.

Causes of raised intracranial pressure in syndromic craniosynostosis

The four principle contributors to raised ICP in children with syndromic craniosynostosis are cranio-cerebral disproportion, hydrocephalus, venous hypertension and airway obstruction.

Cranio-cerebral disproportion

Although it was once thought that a growing brain restrained by a skull restricted in its ability to expand was the principle cause of raised ICP in syndromic synostosis, it is now recognised that this situation is relatively unusual and a reduced intracranial volume (ICV) is an unreliable predictor of raised ICP (Fok et al. 1992; Gault et al. 1992). Indeed in Apert syndrome ICV, although normal at birth, may actually be greater than normal by the time raised ICP declares itself (Gosain et al. 1995; Sgouros et al. 1999). Fortunately the various forms of vault expansion surgery originally designed to increase ICV are equally effective in reducing raised ICP due to a more common cause – venous hypertension (see Raised Venous Pressure).

Airway obstruction

Impairment of the upper airway is common in the severely affected child with syndromic synostosis and is an important contributor to the vicious cycle that determines ICP in these children (Gonzalez et al. 1997). The peaks of ICP that can reduce cerebral perfusion pressure to a mean of around 30mmHg are invariably associated with episodes of airway obstruction during rapid eye movement (REM) sleep. The practical importance of this is that improvement to the airway (see Airway Obstruction) may be all that is needed to reduce the ICP (Fig. 6.10).

Hydrocephalus and the Chiari 1 deformity of in children with syndromic synostosis

Forty per cent may have a degree of ventricular enlargement (Collmann et al. 2005) but in many this is non-progressive. It is important therefore that the craniofacial surgeon does not proceed to treatment – e.g. a shunt insertion – unless ventriculomegaly is worsening and other indicators of raised ICP are present. Hydrocephalus occurs particularly when there is constriction of the skull base and early closure of the lambdoid sutures – which is why it occurs more frequently in Crouzon and Pfeiffer (Types 2 and 3) than in Apert syndrome (Cinalli et al. 1995). Constriction of the skull base, hydrocephalus and raised ICP and herniation of the cerebellar tonsils (the Chiari I deformity) are linked in a cycle of cause and effect (Cinalli et al. 1995; Thompson et al. 1997). The Chiari I deformity is seen particularly in children with a constricted skull base and while its progression (with additional buckling of the lower brainstem) is aided by raised ICP it is also a risk factor for the development of hydrocephalus (de Jong et al. 2012). When tonsillar herniation and brainstem compression in a child with syndromic synostosis becomes symptomatic (when respiratory studies suggest a central as well as an obstructive contribution to breathing problems (Gonzalez et al. 1998) or with the development of syringomyelia, for example) a foramen magnum decompression may be indicated.

Raised venous pressure

Intracranial venous hypertension is a major contributor to raised ICP in children with syndromic synostosis (Hayward
Airway Obstruction

Impaired respiratory function, particularly at night when snoring is a frequent complaint, is a common problem for the more severely affected child with syndromic craniosynostosis. It is usually due to airway obstruction from narrowed nares, crammed nasal passages, a hypoplastic maxilla constricted in all planes and tracheal softening but a central component occurs when there is brainstem compression from a Chiari I deformity (Gonzalez et al. 1998). An airway clear at birth may become obstructed later from tonsillar and (in particular) adenoidal hypertrophy in the restricted pharyngeal space available to them.

In addition to contributing to raised ICP, breathing difficulties impair the ability of the infant and young child to feed and are an important contributor to their failure to thrive. In older children disturbed nights lead to sleepiness during the day and can interfere with schooling.

All children in whom breathing difficulties are suspected should undergo an overnight respiratory sleep study. Although the commonest cause is upper airway obstruction, such a study will determine whether there is a central component, which if associated with a Chiari I deformity may require a foramen magnum decompression (Gonzalez et al. 1998).

Management involves (in ascending order of magnitude) the insertion of a naso-pharyngeal airway (Ahmed et al. 2008), adeno-tonsillectomy (which may need to be repeated as the child grows) (Liasis et al. 2005), continuous positive airway pressure (Gonzalez et al. 1996; Massa et al. 2002), tracheostomy and, finally, operations that open the airway by advancing the maxilla – the LeFort III advance and the monobloc fronto-facial advance (Witherow et al. 2008) with or without distraction.

Vision

Corneal exposure

Recession of the maxilla below and the fronto-orbital region above can leave the corneas exposed and in danger of permanent scarring. Temporary measures to protect them include the instillation of lubricating drops (particularly useful when the eyes do not close completely at night) and tarsorrhaphies although these can raise intraocular pressure when the exorbitis is severe. Longer-term protection requires the advance of the bony orbital rim – either in part (a fronto-orbital advance [FOA]), or complete (an FOA combined with a LeFort III maxillary advance or a fronto-facial monobloc procedure which can in exceptional circumstances be performed in the very young [Britto et al. 1998]).

The vision of children with syndromic craniosynostosis can be affected also by raised ICP, astigmatism and amblyopia. In one assessment of visual acuities in children with syndromic craniosynostosis 40% had function in their better eye below a level (6/12) that would allow them to hold a driving licence in the United Kingdom (Khan et al. 2003) a proportion of which morbidity can be attributed to raised ICP.

Failure to Thrive

Regardless of any contribution from the disordered gene, severe breathing difficulties due to a combination of airway obstruction and any central depression of respiration can so interfere with feeding that the affected child may fail to gain weight – or even lose it. A dyspraxia of oro-pharyngeal movements may also contribute.

Adjuvent feeding of infants via a naso-gastric tube and occasionally a gastrostomy may be required but the most dramatic improvements are seen following procedures aimed at restoring a more effective airway.
Part III  Neurological Consequences of Prenatal, Perinatal and Early Postnatal Interference with Brain Development

Developmental Delay/Learning Difficulties
Developmental delay, learning difficulties and a wide range of cognitive issues can affect the child with craniosynostosis including those with no more than single suture involvement. While many may be related to effects of the disordered gene (and particularly any associated chromosomal abnormality), an important role of the multidisciplinary craniofacial unit is to manage any potentially remedial causes that can also contribute. These include hydrocephalus, chronic airway obstruction, feeding difficulties and ‘failure to thrive’, the developmental consequences of impaired vision and/or hearing and the effects of low societal and family expectations (including teasing). Experienced input is needed to ensure that such problems are recognised early and appropriate therapy instituted at an age when it is most likely to be of benefit.

Epilepsy is rare in craniosynostosis but has a higher than expected incidence in Muenke (Agochukwu et al. 2012) and Apert (Agochukwu et al. 2012) syndromes, in children with the fetal valproate syndrome and those with associated chromosomal abnormalities. It may also occur as a post-operative complication, a consequence of the frontal lobe retraction required during fronto-facial monobloc and biparietirion procedures in children with severe frontal bone recession (Cobb et al. 2013).

Cosmesis
The cosmetic disabilities that most trouble patients with syndromic synostosis and their families include a misshapen forehead, eyes that protrude, eyes set too far apart (hypertelorism) and an upper jaw set back while the lower jaw protrudes.

When correcting for cosmesis alone it is important to remember that surgery carried out on a part of the craniofacial skeleton that is still growing may need to be repeated either wholly or in part in order to achieve a result that will prove stable over time. Our own policy, based more on clinical observation than measurement, is to assume that a forehead and supra-orbital region in a satisfactory configuration at around 10 years of age is unlikely to need further correction and essentially cosmetic reconstructions after that age can focus more on the maxilla and mandible where growth will continue until secondary dentition is complete – the mid to late adolescence.

Primary craniosynostosis whether it affects one or multiple sutures and is associated or not with a particular syndrome is rare and its management should only be undertaken by a unit with sufficient experience to ensure affected children achieve their developmental potential.

Early assessment by such a unit will enable the correct diagnosis (both genetic and clinical) to be made, the risk of complications assessed and a management plan made that is tailored to each individual child’s needs.

While in non-syndromic unisutural synostosis treatment may require no more than a single reconstructive operation, more complex cases require input from a wide range of specialists including the paediatric neurologist often until the completion of skeletal maturity.

Disorders of the Craniovertebral Junction
Disorders of the craniovertebral junction (CVJ) in childhood occur in the context of a seemingly overwhelming array of congenital and acquired disorders, some not uncommon (e.g. Down syndrome) others exceedingly rare (e.g. metabolic bone diseases). The nosology and classification of skeletal disorders has recently been revised by the International Skeletal Dysplasia Society (Warman et al. 2011). The precise nature of the CVJ anomaly and its natural history vary according to the underlying disease. These factors are further complicated by the inevitable difficulties in neurological evaluation of the infant and young child, particularly those with co-existing musculoskeletal and cognitive impairments. Choosing the correct investigations and determining an appropriate management strategy is thus complex and a not infrequent source of confusion.

This chapter presents a simple mechanistic approach that can be applied to almost all craniovertebral anomalies. This approach serves to aid selection of particular diseases or syndromes that may require specific evaluation of the CVJ, guide appropriate investigation and determine a logical treatment pathway. Some of the more frequently encountered CVJ disorders are selected for more detailed discussion.
the normal and abnormal development of the craniovertebral junction can be found elsewhere (Pang and Thompson 2011). While osseous malformations of the CVJ are found in isolation in clinical practice, they will more commonly occur in the context of a recognised syndrome or bone dysplasia. Existing classifications according to syndrome type, metabolic anomaly, genetic aberration etc. have their limitations and for the most part offer no practical guidance to the physician. A simple mechanistic approach is suggested that will alert the clinician to those particular diagnoses that are at risk of CVJ anomalies, indicate the likely clinical manifestations that might result and serve as a guide to the most appropriate initial investigations. While the final management plan and surgical intervention will be the province of the specialist it is hoped that this practically oriented approach will permit early referral where appropriate and act as a template for ongoing surveillance.

An understanding of the basic anatomy of the CVJ and the terms commonly used to describe its disorders is pertinent to subsequent discussion.

ANATOMY OF THE CRANIOVERTEBRAL JUNCTION

The posterior skull base is formed by the occipital bone. The occipital bone has a flattened squamosal portion that contributes to the posterior fossa and provides the large surface area for attachment of the suboccipital musculature, a ventral portion that forms the lower third of the clivus and, between these two, the occipital condyles (for articulation with C1). Together these structures form the boundaries of the foramen Magnum. The first cervical vertebra (atlas), a ring shaped structure, acts as a ‘washer’ between the occipital bone and the second cervical vertebra (axis). These ‘atypical’ vertebrae are modified to permit rotation at the CVJ, which is the primary movement at C1/C2. In contrast, that between the occiput and C1 is flexion/extension (Steinmetz et al. 2010). The atlas lacks a vertebral body. Instead the odontoid peg, a rostral extension of the body of the axis, projects into the ring of the atlas vertebra. Here it articulates by means of a small synovial joint between its tip and the inner surface of the anterior ring of the axis. The odontoid is held in place, within the ring of the axis by means of the transverse ligament, a strong structure that extends from one side of the atlas to the other. Additional ligaments (apical and alar) extend from the tip of the odontoid peg to attach to the anterior margin of the foramen magnum. It is the structural integrity of these ligaments that ensure that the odontoid can act as a pivot to permit rotation while preventing backwards movement toward the spinal cord.

EXPLANATION OF TERMS USED IN DESCRIBING CRANIOVERTEBRAL JUNCTION

The nomenclature surrounding CVJ anomalies can lead to confusion. The following terms warrant clarification.

Os Odontoideum

The rostral part of the odontoid peg may become detached from its base thus resulting in a bipartite odontoid (Fig. 6.12). The separate ossicle of bone, os odontoideum, remains attached to the foramen magnum by the apical and alar ligaments. However, since the os is functionally separated from the rest of the axis, the transverse ligament is rendered incompetent leading to atlanto–axial instability. During flexion the base of the odontoid, now unchecked, can move posteriorly into the cervical canal and compress the spinal cord. Traditionally considered to be a developmental anomaly, it is now more widely accepted that os odontoideum is a result of an early, ununited fracture through the base of the odontoid (Crockard and Stevens 1995; Arvin et al. 2010). Os odontoideum is particularly well recognised in Down syndrome; in one series 10 of 12 children with Down syndrome who required surgery for symptomatic atlanto–axial subluxation had os odontoideum (Nader-Sepahi et al. 2005). The os may thus be a consequence as well as a cause of instability.

Platybasia

The term platybasia refers to the obtuse angle formed by the anterior cranial fossa with the slope of the clivus. This angle may range from 115° to 130°; however, the normal range can vary significantly depending on the measuring technique and imaging modality used (Koenigsberg et al. 2005) and so these need to be standardised when making comparisons or clinical inference. While the basal angle has important anthropological relevance it has a limited use in clinical practice.

In the past, various craniometric measures with eponymous names (Chamberlain’s line, McGregor’s line and Wackenheim’s line) were devised, usually based on plain X-rays, in an attempt to infer the effects of craniovertebral deformity on the underlying neuraxis (Smoker and Khanna 2008). The advent of MRI permitted clearer demonstration of compression or distortion of the brainstem or spinal cord thus largely obviating the need for such measurements.
Basilar Invagination and Basilar Impression

These two terms are often used interchangeably to describe situations in which the odontoid peg projects above the plane of the foramen magnum (Smith et al. 2010). More precisely, most authors use basilar invagination to describe a primary form in which there is upwards migration of the upper cervical spine into the foramen magnum in the context of congenital anomalies such as assimilation of the atlas and vertebral segmentation defects. While basilar impression, or secondary basilar invagination, is used in the presence of bone softening conditions, such as Paget disease, osteogenesis imperfecta or Hadju-Cheney syndrome resulting in an in-folding of the entire skull base (Sawin and Menezes 2009).

Basilar invagination can result in compression of the brainstem and distortion of the posterior fossa structures leading to herniation of the hindbrain through the foramen magnum (Chiari Type I) in up to half of patients (Goel et al. 1998). Conventional foramen magnum decompression alone is often insufficient treatment for Chiari Type I in this context (Greenlee et al. 1999; Kim et al. 2004).

Table 6.2 Disorders of the craniovertebral region in childhood

<table>
<thead>
<tr>
<th>Condition</th>
<th>Underlying genetic or metabolic cause</th>
<th>Instability</th>
<th>Deformity</th>
<th>Neuraxial compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Trisomy 21</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>FGFR3</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>COL1A1, COL1A2</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Spondylo-epiphyseal dysplasia</td>
<td>COL2A1</td>
<td>+++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Klippel-Feil (segmentation anomalies)</td>
<td>Heterogeneous, includes GDF3 and GDF6</td>
<td>+</td>
<td>+++</td>
<td>_</td>
</tr>
<tr>
<td>Morquio syndrome</td>
<td>Lysosomal storage disorder</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Larsen syndrome</td>
<td>Filamin B</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Atlanto–axial rotatory fixation</td>
<td>Acquired</td>
<td>–</td>
<td>+++</td>
<td>–</td>
</tr>
</tbody>
</table>

–, not associated; +, may occur; ++, commonly occurs; ++++, typically associated. *Compression rarely occurs in childhood, but may occur in young adulthood due to degenerative changes at the remaining mobile segments.

Platyspondyly

This term refers to the flattened or bullet shaped vertebral body that typifies some of the metabolic bone disorders such as spondyloepiphyseal dysplasia and Morquio disease.

BIOMECHANICAL CONSIDERATIONS

There are, in essence only three biomechanical problems at the CVJ that are of clinical relevance: these are instability, deformity and compression of the neuraxis. These can occur in isolation or in any combination. Certain conditions have a predilection for particular biomechanical problems; e.g. instability is a characteristic of Down syndrome, focal compression at the foramen magnum is seen in achondroplasia and deformity is the main issue in disorders of cervical segmentation.

Table 6.2 summarises the principle biomechanical deficiencies occurring at the CVJ in various dysplasias, syndromes or diseases.

Instability

The stability of the CVJ is maintained by osseous, ligamentous and muscular factors. Where these are compromised by congenital or acquired disorders movement may exceed the normal physiological limits and pose a risk to the underlying neuraxis. Instability may occur at the occipito–atlantal joint, the atlanto–axial joint or in the sub–axial spine. Pure occipito–atlantal instability is rare and quite a difficult to confirm radiologically, particularly in young children. (Karol et al. 1996) Occipito–atlantal instability occurs in combination with atlanto–axial instability in Down syndrome. Morquio syndrome and spondyloepiphyseal dysplasia are also particularly prone to CVJ instability.

INVESTIGATING INSTABILITY

Atlanto–axial instability (AAI) is best assessed using a dynamic technique and the most appropriate investigation is plain lateral cervical spine X-rays performed in flexion and extension (Fig. 6.13). Instability is almost always accentuated in flexion; however, the extension view is important to assess whether any instability is reducible by restoration of the normal relationship between the odontoid peg and the anterior arch of the atlas.

The traditional measure of instability is the atlanto-dental interval (ADI), the distance between the odontoid peg and the anterior arch of the atlas measured in flexion (normal <5mm). An additional measure of AAI is the neural canal width (NCW) or posterior atlanto-dental interval (PADI).
This is the distance between the back of the odontoid peg and the anterior surface of the posterior atlantal arch. It is thus a measure of the space available for the spinal cord. White et al. (1993) measured ADI and NCW in both plain X-rays and MRI in patients with Down syndrome; they found that NCW but not ADI correlated well with subarachnoid space available for the spinal cord.

While flexion and extension CT and MRI are feasible, the range of excursion in neck movement that is achievable is less than with plain X-rays and so these tend only to be used when there is associated deformity that compromises interpretation of plain X-rays. Furthermore, dynamic studies should only be performed in awake patients therefore, in children requiring general anaesthetic for CT or MRI a dynamic study is contra-indicated.

Deformity
If instability is defined as movement in excess of the normal physiological range, then deformity can be considered as alignment outside the normal range. Deformity at the CVJ may occur as a result of distorted normal anatomy (rotational deformity or sagittal deformity) or as a consequence of anomalous segmentation.

Rotational deformity
The clinical presentation is with torticollis. This is a combination of lateral head tilt and rotation resulting in the ‘Cock Robin’ deformity. The differential diagnosis of torticollis in childhood is wide including tumour, infection, trauma and vascular (Per et al. 2014); however, there are two particular conditions that are important to diagnose as they are amenable to surgical intervention.

The first, tight sternomastoid, is a condition that commonly dates back to infancy. There may be a history of birth trauma or unilateral neck swelling during the neonatal period (Cheng et al. 2000). This swelling, often called a ‘sternomastoid tumour’, is a haematoma of the muscle that resorbs, leaving a fibrotic contraction of the muscle. This results in a taut band along the line of the muscle. The treatment is division of the sternomastoid muscle and fibrotic band, a procedure that has low risk and favourable cosmetic improvement in most patients (Shim et al. 2004).

The second, atlanto–axial rotatory fixation (AARF), is an acquired condition, presenting in older children, in which there is fixed malalignment between C1 and C2 (see below).

Sagittal deformity
The normal lordotic curvature of the cervical spine complements the normal thoracic kyphosis and lumbar lordosis resulting in an overall balanced sagittal spinal profile. In some circumstances the cervical curve reverses, resulting in kyphosis or forward bending of the cervical spine. The craniocervical junction, instead of lying along the sagittal profile, assumes a more anterior position that compromises biomechanical stability with a tendency to progressive deformity. This is the classic appearance in Larsen syndrome (Sakaura et al. 2007). The onset of deformity is usually in infancy and may progress with myelopathy (Johnston et al. 1996). The timing of surgery can be problematic given the technical constraints associated with spinal fusion in young children.

Segmentation anomalies
Segmentation of the somitic mesoderm takes place in the third week of embryonic life. Segmental identity of the various vertebrae is conferred by the differential expression of Hox genes (Pang and Thompson 2011). Failure of segmentation may occur as a result of an underlying genetic mutation in a wide number of genes (Giampietro et al. 2008), though in many cases is likely to result from an early teratogenic insult (Giampietro et al. 2013). Maternal diabetes (Åberg et al. 2001), alcohol (Tredwell et al. 1982) and anticonvulsant use...
(Holmes et al. 2001) are among the teratogens associated with cervical segmentation anomalies. Broadly speaking, two types of segmentation anomaly are encountered: anomalies of fusion and anomalies of form.

**Anomalies of fusion (Klippel-Feil deformities)**
In these there is a failure of intervertebral disc development resulting in block vertebrae (Fig. 6.14). The classic clinical description is a triad of short neck, low posterior hairline and reduced neck movements. Common sites of fusion are between the occiput and atlas (atlanto-occipital assimilation) and C2/3, although much longer segments of fusion are well recognised (Clarke et al. 1998; Samartzis et al. 2006). This is an etiologically diverse entity and dominant, recessive and X-linked modes of inheritance have been described. Anomalies of fusion frequently occur in the syndromic craniosynostoses (Thompson et al. 1996).

**Anomalies of form**
In contrast to anomalies of fusion, where the number of mobile segments is reduced, in anomalies of form it is the shape of the vertebrae that is abnormal. Examples include butterfly vertebrae, hemivertebrae and sometimes irregular shapes that do not fit in with conventional descriptions. In these children the neck is typically short and the range of movement reduced as with Klippel-Feil syndrome; however, torticollis is more evident. Associated features include orbital and ocular anomalies as well as abnormalities of branchial arch development including micotia, preauricular sinuses and skin tags. The clinical spectrum includes the eponymous conditions Goldenhaar and Wildervanck; however, it is now recognised that considerable overlap exists and the term oculo-auriculo-vertebral spectrum (OAVS) is perhaps more clinically useful (Gorlin et al. 2001).

Anomalies of fusion and anomalies of form.

**Investigating deformity**
Plain X-rays are rarely of use in the investigation of craniovertebral deformity as any rotational component makes interpretation difficult. High resolution CT is a much more appropriate tool with which to evaluate the bony anatomy. In additional to conventional axial views the data can be reformed in sagittal and coronal planes, as well as 3D, to provide additional information regarding alignment and its effect on the spinal canal (Newton et al. 2002). CT is useful in planning elements of instrumentation surgery such as screw size and trajectory or for intra operative image guidance. Additionally CT angiography (CTA) can be particularly helpful to assess the course of the vertebral arteries which may be altered by congenital or acquired deformity (Barker et al. 2009).

**Neuraxial Compression**
Stenosis at the foramen magnum, skull base malformation or narrowing of the cervical spinal canal due to anomalies of the atlas or axis can result in effacement of the normal
CSF spaces and direct compression of the brainstem or spinal cord. The incidence of Chiari I malformation in patients with CVJ malformations is estimated to be between 33 and 38% (Menezes 2012). It should be noted that the descent of the cerebellar tonsils that characterise the Chiari I malformation is not a true malformation but rather a deformity of the neuraxis in response to the local bony anatomy. It is now widely acknowledged that the bony malformation leads to reduced posterior fossa volume and thus secondary herniation of the cerebellar tonsils (Badie et al. 1995; Sgouros et al. 2006; Trigylidas et al. 2008). Therefore, the terms cerebellar tonsillar ectopia or hindbrain hernia are perhaps more appropriate.

**Investigating neuraxial compression**

MRI is the imaging modality of choice in the evaluation of suspected neuraxial compression and the most appropriate modality for the surveillance and screening of craniovertebral anomalies in the bone dysplasias; e.g. Morquio and achondroplasia (Kao et al. 1989; Janus et al. 2003; Smoker and Khanna 2008).

**Clinical presentation of craniovertebral anomalies in children**

Specific patterns of biomechanical compromise are characteristic of particular CVJ abnormalities (Table 6.2). This will aid in focusing the history and examination.

**History**

The phenotype of many bone dysplasias and metabolic bone disorders will include short stature, joint contractures or laxity, reduced muscle bulk and generalised motor delay. These features will impact on the clinical presentation and neurological examination findings; it is important therefore that symptoms and signs are interpreted in context. With this in mind a history of recent change in functional ability, loss of previously acquired motor skills, increasing tendency to fall or worsening balance may be features of emerging myelopathy.

Symptoms of bulbar dysfunction should be specifically sought. In children with CVJ or high cervical abnormalities, brainstem compression may occur both in response to direct compression of the neuraxis by the bony malformation (e.g. in the basilar invagination of osteogenesis imperfecta) or as a consequence of the associated Chiari I malformation (e.g. in cases of atlanto-occipital assimilation). Overt or subclinical respiratory dysfunction is commonly overlooked in both adults and children with cranial vertebral junction anomalies. Respiratory sleep studies may be helpful in the investigation of selected cases. Botelho et al. (2003) found that the incidence of sleep apnoea and hypopnea syndrome were significantly higher in patients with CVJ malformation compared with controls. A history of poor sleep, snoring and morning tiredness and headache may be significant.

Pain is a common presenting feature with occipital, neck or cervical pain being present in 85% cases of CVJ abnormality. The combination of posterior headache with brainstem or cerebellar features such as ataxia, vertigo, hyperacusis or tinnitus is referred to as basilar type migraine and has been reported in 25% of children with basilar invagination (Menezes 2008).

**Examination**

Features of myelopathy are the commonest clinical findings in symptomatic craniovertebral anomalies and are present in as many as 85% of patients (Menezes 2008). Cranial nerve dysfunction is also well recognised. Menezes (2008) reported that hearing loss was the commonest cranial nerve deficit, occurring in 23% of cases. Lower cranial nerve dysfunction, sometimes in combination with brainstem compression, can produce reduced gag reflex and poor oropharyngeal co-ordination leading to dysphagia or aspiration. Video swallow studies may identify particular patients at risk. Bulbar electromyography similarly can be of help in selected cases.

Neck position and range of movement are often abnormal in CVJ anomalies. The short neck with reduced range of motion is characteristic of segmentation disorders while a fixed torticollis posture implies asymmetry as seen in cervical hemivertebrae, partial atlanto-occipital assimilation or atlanto-axial rotatory fixation.

**Specific diseases associated with craniovertebral anomalies**

Spinal involvement and neurological compromise are features of many of the skeletal dysplasias (Song and Maher 2007; McKay et al. 2012). The following conditions are among the more commonly encountered and exemplify particular aspects of craniovertebral disease.

**Down syndrome**

Atlanto-axial instability is the most prevalent craniovertebral anomaly in Down syndrome; however, there has been considerable controversy surrounding the role of routine radiological screening, the threshold for surgical intervention and the necessity to curtail physical activities (Pueschel 1998; Brockmeyer 1999). Studies in Down syndrome have cast some doubt on the utility of cervical spine radiographs in the routine evaluation of atlanto-axial instability. Firstly, there is no consensus on what ADI distance (the conventional radiological measure of instability, see Investigating Instability) constitutes a diagnosis of atlanto-axial instability nor indeed what distance constitutes a threshold for concern, with authors using from 3mm to 6mm. Secondly, the natural history of atlanto-axial instability in Down syndrome is unclear with some longitudinal studies suggesting a trend toward
decreasing ADI over time (Pueschel and Scola 1987; Morton et al. 1995), while others have reported the opposite (Burke et al. 1985). Indeed in one study, radiographs performed on the same day yielded differing results for ADI in six of 19 children leading the authors to conclude that X-rays were an unreliable means of diagnosing AAI and their use could not be supported as a screening test (Selby et al. 1991). A further factor is the prevalence of atlanto–axial instability in Down syndrome and its poor correlation with symptoms. Between 10–20% of individuals with Down syndrome will have radiological evidence of AAI, yet only 1–2% have clinical symptoms that might be attributed to this (Pueschel and Scola 1987; Pueschel et al. 1992). In one study of 84 patients with Down syndrome, 17 had radiological evidence of subluxation among whom there were five with symptoms. By contrast, in the 67 without subluxation 18 had symptoms (Ferguson et al. 1997). The available evidence therefore suggests that in Down syndrome the correlation between instability as measured by ADI and neurological symptoms is far from clear. Current UK guidelines advise against routine radiological screening for AAI in the population with Down syndrome but emphasise the importance of raised awareness of the potential for cervical spine disease in this group and the recognition of warning symptoms such as cervical pain, head tilt, limb weakness and gait disturbance. (For current UK guidelines go to www.dsmig.org.uk.)

ACHONDROPLASIA

Narrowing of the entire spinal canal is a characteristic of achondroplasia. However, it is stenosis at the foramen magnum that presents most commonly in childhood and is the most frequent reason for neurosurgical intervention in this age group, hydrocephalus being the second (King et al. 2009). The clinical presentation of foramen magnum stenosis is weakness with regression of motor milestones and hyperreflexia in the limbs. Respiratory symptoms of disordered breathing, snoring or apnoea are present in almost half of cases requiring surgery (Bagley et al. 2006) and may be both obstructive and central in origin (Aryanpur et al. 2009). Respiratory sleep studies are now recommended as part of the regular evaluation of these children (Julliand et al. 2012). Sudden unexpected death is well recognised in this population. In one study, five out of 11 children who died suddenly were found to have cervico-medullary compression (Pauli et al. 1984). Where obstructive respiratory symptoms predominate adenotonsillectomy should be considered prior to craniovertebral decompression.

Foramen magnum stenosis in achondroplasia begins in infancy and radiological evidence of stenosis is present in up to 70% of infants in some case series (Reid et al. 1987; Pauli et al. 1995), although symptoms or signs of cervicomedullary compression were present in only 15–35% of patients in these studies. It is thus important to recognise that potentially significant stenosis may develop without obvious symptoms and thus spinal MRI is recommended within the first year or so of life even for asymptomatic individuals (Keiper et al. 1999). MRI findings include narrowing in both the coronal and sagittal planes due to a combination of bone and ligamentous thickening, effacement of CSF spaces and signal change within the medulla or spinal cord (Fig. 6.15). True craniovertebral instability is rare in achondroplasia; however, due to the narrow foramen magnum even the normal range of motion may be sufficient to cause dynamic cervicomedullary compression in these children (Mukherjee et al. 2014). While dynamic MRI is not part of the routine evaluation of these children it should be considered in children who have clinical symptoms without overt compression on static MRI.

Eighty per cent of craniovertebral decompressions in achondroplasia are deemed necessary within the first 5 years of life (Aryanpur et al. 2009; King et al. 2009). Marked thickening of the bone, a deep occipital keel and unusually medial position of the vertebral arteries pose specific surgical challenges in achondroplasia, and while surgery will result in neurological and respiratory improvement in the majority of cases strict clinical and radiological criteria need to be applied to the selection of cases (Reina et al. 2014).

MORQUIO SYNDROME AND THE MUCOPOLYSACCHARIDOSES

Involvement of the CVJ and cervical spine is a feature of mucopolysaccharidoses (MPS; see Chapter 9): MPS IH (Hurler), MPS IH-S (Hurler Scheie), MPS1-S (Scheie), MPS II (Hunter) and MPS VI (Morateaux-Lamy); however, it is in Morquio syndrome (MPS-IV), the commonest of the MPS disorders, that craniovertebral involvement is particularly
prevalent and responsible for significant morbidity and mortality. Spinal abnormalities are mild or absent at birth but appear within the first 2 years of life and are progressive thereafter.

The characteristic radiological changes include odontoid hypoplasia, extradural soft tissue thickening (due to infiltration with glycosaminoglycans), platyspondyly and ligamentous laxity (Hughes et al. 1997; Solanki et al. 2013a). These changes result in CVJ instability in at least half of cases (Harmatz et al. 2013). Spinal cord damage occurs secondary to atlanto–axial instability and compression from a narrow C1 and may become severe without obvious clinical symptoms or signs. Rapidly evolving myelopathy or sudden tetraparesis are well recognised thus emphasising the need for regular radiological surveillance (spinal MRI and dynamic X-rays) from infancy (Solanki et al. 2013b). Progressive radiological changes, signal change within the spinal cord or emerging neurological symptoms are the usual indications for surgery (Fig. 6.16). As a result of the particularly high incidence of craniovertebral involvement in this disease coupled with improved surgical outcome in children prior to the development of myelopathy some authors have recommended prophylactic fusion in this group of children (Ransford et al. 1996). Surgery, therefore, tends to be required early in children with Morquio disease. The mean age at surgery was 5 years 3 months in one recent large series (Dede et al. 2013) and this would be in keeping with the authors experience. Surgery typically entails decompression (removal of the posterior arch of C1) and concomitant fusion from the occiput to C2. Successful fusion can be anticipated in the majority of patients however, there remains a risk of late deformity or junction instability, i.e., increased movement at remaining mobile segments adjacent to the fused segment (Dede et al. 2013).

While enzyme replacement therapy (see Chapter 9) has had beneficial effects on the systemic aspects of MPS I (and its subtypes), II and VI (Desnick 2004), there is currently no evidence that it halts the progression of spinal disease.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta is a disorder of Type I collagen synthesis. OMIM currently lists 13 types of osteogenesis imperfecta (OMIM 2014). The majority are due to mutations in either COL1A1 or COL1A2 genes. The CVJ anomaly associated with osteogenesis imperfecta is progressive basilar invagination and is a particular feature of osteogenesis imperfecta types III and IV. Clinically significant basilar invagination is rare in the first decade, the symptom onset tends to be in adolescence or young adult years (Ibrahim and Crockard 2007; Sawin and Menezes 2009).

Presentation is with headache and cranial nerve dysfunction which were present in 76% and 68% respectively in the series described by Sawin (Sawin and Menezes 2009). Hydrocephalus was present in 32%. Trigeminal neuralgia due to stretching of the Vth nerve is also common (Hayes et al. 1999).

Neurosurgical treatment is reserved for symptomatic cases. Because of the basilar invagination surgery will often necessitate anterior decompression as well as posterior fixation and thus surgical morbidity can be significant. Timing of surgery is important. In expert hands stabilisation or symptomatic improvement can be anticipated so long as intervention is carried out early in the evolution of symptoms (Ibrahim and Crockard 2007).

Intravenous infusions of disodium pamidronate have been shown to improve bone density and reduce the incidence of fractures in patients with osteogenesis imperfecta. There is some evidence that treatment commenced early in childhood may prevent basilar invagination (Aström et al. 2007).

SPONDOLOEPIPHYSEAL DYSPLASIA

Spondyloepiphyseal dysplasia (SED) is an autosomal dominant chondrodysplasia, characterised by dwarfism, barrel chest and limb shortening with coxa vara, though with normal sized hands and feet. It is a disorder of Type II collagen. Allied disorders include Kniest dysplasia and Strudwick dysplasia and in each there is hypoplasia of the odontoid and ligamentous laxity that predisposes to atlanto–axial instability.

Children with the early onset form of the disease (SED congenita) are more severely affected and at greater risk of myelopathy. Atlanto–axial instability tends to worsen over time (Miyoshi et al. 2004). The sagittal diameter of the spinal canal is often narrowed at the level of the atlas, even after reduction of instability due to abnormal shape of the posterior arch of the atlas; C1 laminectomy is therefore commonly required at the time of occipitocervical fixation (Nakamura et al. 1998).
In contrast to the other conditions described in this chapter, atlanto–axial rotatory fixation (AARF) is an acquired abnormality; however, it is included here as it is an anomaly of the craniovertebral region that is almost exclusively seen in the paediatric population and is a common cause of missed or delayed diagnosis (Schwarz 1998). The clinical presentation is with torticollis, the ‘Cock Robin’ appearance of rotation and lateral flexion. This is initially painful though pain may settle over a period of a few days. A prior history of upper respiratory tract infection or tonsillitis (Grisel syndrome) or onset following anaesthesia (particularly for ENT procedures) is well described (Deichmueller and Welkoborsky 2010). In some cases there may have been minor trauma or some predisposition to ligamentous laxity, for example Down syndrome, though in one-quarter of cases no apparent cause can be identified. Neurological injury is exceedingly unusual, as the adjacent ligaments remain competent.

The pathophysiology of AARF relates to excessive rotation of C1 with respect to C2. The degree of rotation and the presence of any residual movement at the joint form the basis of the original classification for this disorder by Fielding and Hawkins (1977) more recently refined by Pang and Li (2005a). Establishing the diagnosis requires dynamic high resolution CT performed in the position of deformity, the neutral position and after attempted contralateral movement (Fig. 6.17). In simple muscular torticollis realignment will be demonstrated whereas in AARF the relative positions of C1 and C2 remain abnormal despite neck turning.

Some cases resolve spontaneously or with the use of regular muscle relaxants and analgesia. For cases that fail to respond to these simple measures treatment must be escalated. The majority of cases can be successfully reduced by manipulation under anaesthesia or application of halo traction. Once anatomical reduction is achieved the neck needs to be immobilised in halo-body orthosis for up to 3 months. In cases that present late chronic subluxation may develop reducing the chances of successful reduction and increasing the risk or recurrence and the need for definitive surgical fusion between C1 and C2 (Pang and Li 2005b).

### TREATMENT OF CRANIOVERTEBRAL JUNCTION DISORDERS

The principles underlying the management of craniovertebral disorders in children can be summarised as follows (Table 6.3).

#### Restoration of Normal Alignment

This may be achieved through skeletal traction, reduction under anaesthesia or incremental traction in a halo-body jacket. This latter technique can be useful in young patients unable to tolerate conventional skeletal traction; a halo-body orthosis is applied that is then distracted at intervals until optimal alignment is achieved.

#### Decompression of the Neuraxis

Where the brainstem or spinal cord is compressed after restoring normal alignment then decompression is indicated. This will most commonly be performed through a posterior approach; however, where there is ventral compression a transnasal or transoral approached will be indicated in addition (Hankinson et al. 2010).

#### Stabilisation of Unstable Segments

When there is instability, either as a result of the underlying disease or as a consequence of surgical decompression, then internal fixation will be required. A variety of techniques are available using autologous bone or instrumented fixation. The extent of fixation (e.g. whether or not to include the occiput) will depend on the underlying pathology and age of the child, but in general terms the aim is to keep fusion segments as short as feasible in order to optimise long-term mobility.
NORMAL VARIANTS OF THE CRANIOVERTEBRAL JUNCTION

There are a number of radiological variants that occur in the craniovertebral region that are a common source of anxiety for the parent and physician but which are either within the range of normal or do not have clinical significance.

OSSICULUM TERMINALE

Also known as Bergman ossicle, this is a small bony structure sometimes seen at the apex of the odontoid process. It is considered to be a developmental remnant that would ordinarily have formed the tip of the dens. It is readily distinguishable from a dens fracture. Its margins are usually smooth and well corticated, it is smaller than an os odontoideum and in contrast to the latter it has no implications in terms of instability.

C2/3 PSEUDO SUBLUXATION

Apparent forward displacement of the body of C2 with respect to C3 is commonly seen in paediatric patients. In one study 46% of children under 8 years had evidence of ‘pseudo-sUBLUXATION’ (Cartell and Filtzer 1965) on cervical X-rays. This appearance commonly raises concerns about stability particularly in cervical spine X-rays performed after trauma. The absence of bony fracture, the mechanism of trauma and absence of clinical features of neck pain or tenderness are usually sufficient to allay anxiety.

ATLAS ANOMALIES

Anterior or posterior spina bifida at C1 is a normal finding in children up to 4 years of age and represents incomplete ossification of the C1 ring and has no sinister connotations. Such abnormalities can persist beyond this age, e.g. in Down syndrome. Rarely, there is complete absence of the posterior arch of C1 which, in the absence of clinical symptoms, is not usually significant as the transverse ligament remains competent.

A wide variety of musculoskeletal syndromes commonly involve the craniocervical region. The prevalence and pattern of craniovertebral involvement can often be predicted according to the underlying genetic syndrome or skeletal dysplasia. This in turn can help to determine the appropriate level of clinical surveillance and the most relevant radiological investigations. A management strategy can then be formulated that takes into account the perceived natural history of the disorder, the skeletal maturity of the child and the protection of the neuraxis.

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Hydrocephalus and Non-Traumatic Pericerebral Collections

Andrew Whitelaw and Christian Sainte-Rose

Hydrocephalus is one of the most important conditions in paediatric neurology because treatment can prevent, reduce or limit brain injury and disability. Although treatable, hydrocephalus is a chronic disorder, responsible for 69,000 hospital admissions annually in the United States and accounting for three times as many hospital days and dollars as cystic fibrosis (Simon et al. 2009). This chapter will consider all types of hydrocephalus from fetal life to late childhood and, for convenience, will cover non-traumatic pericerebral fluid collections.

DEFINITION OF HYDROCEPHALUS

Hydrocephalus means an excess of fluid within the cranium. However, it is customary to reserve the term for the condition in which the volume of cerebrospinal fluid (CSF) is increased in all or part of the intracranial fluid spaces, and is not the result of primary atrophy or dysgenesis of the brain. The abnormal accumulation of CSF is associated with increased pressure, at least in the initial stages of the disorder.

PHYSIOLOGY OF CSF

The greater part of the CSF is secreted actively by the choroid plexus. Experiments in animals indicate that 35% or more of the CSF, depending on species, may come from extraplexic sources. In humans, it is estimated that 70–90% of the fluid originates from the choroid plexus (McComb 1983); the remainder originating in brain parenchyma as a result of exchanges with cerebral extracellular spaces.

Rate of CSF Production

The daily formation of CSF in children and adults is about 500ml. The night and day rhythm of secretion is relatively stable and amounts to 0.35ml/min in adults. The total volume of CSF in the head of an adult is about 120ml, and the average ventricular volume is around 25ml, although individual variations occur. In the neonate, CSF volume is about 50ml.

CSF Resorption

Most of the CSF is resorbed passively through the subarachnoid villi (granulations of Pacchioni) along the superior sagittal sinus, into the sinus blood flow. The CSF pressure is normally greater than venous blood pressure. A pressure gradient of 20–50mm H₂O is necessary to allow resorption into the venous sinuses through the arachnoid villi. Three additional mechanisms...
for CSF re-absorption have been proposed: (1) an energy-consuming pinocytotic process by which intracytoplasmic vacuoles are transported from one side of the arachnoid membrane to the other; (2) transport via olfactory nerves, cribriform plate and nasal lymphatics (Koh et al. 2005); and (3) transepndymal absorption across brain tissue into blood vessels (Greitz and Hannerz 1996). The villi in the arachnoid granulations provide a greatly increased surface area available for re-absorption. However, newborn infants do not have visible arachnoid granulations nor any arachnoid villi on microscopy. The absence of such structures may mean that CSF is absorbed by other routes in the neonate or that maximum capacity for re-absorption is less than in the adult. A significant amount of CSF may be resorbed via cervical lymph vessels (McComb 1983) and via the spinal cord (Koh et al. 2005). This pathway may be of importance in hydrocephalus.

CSF Pressure

The hydrostatic pressure of the CSF (synonymous with intracranial pressure [ICP]) is determined by the CSF secretion pressure and from the resistances to its circulation and resorption. Normal intracranial (or CSF) pressure at the level of the foramen of Monro is 100–150mmH2O in children and adolescents at rest in the lying position. In the newborn infant, CSF pressure is lower, around 40–50mmH2O (Kaiser and Whitelaw 1986).

PATHOPHYSIOLOGY OF HYDROCEPHALUS

Except in the rare cases of CSF hypersecretion, hydrocephalus is virtually always due to an increase in the resistance of CSF circulation pathways resulting in an increase in CSF pressure. Table 7.1 lists the various sites and mechanisms by which this may occur.

Increased resistance may be located within the ventricular system, in the posterior fossa, in the cisterns or subarachnoid spaces or at the sites of resorption. CSF flow is a function of the difference between CSF and venous sinus pressures, divided by the resistance of pathways. As CSF production is stable over a relatively wide range of pressures, an increase in CSF pressure is inevitable when there is impaired absorption. The magnitude of the effects of this increase in pressure will depend largely on the yield pressure or compliance of the brain and skull.

Low versus High Compliance

When the brain and skull are highly compliant (low yield pressure), there is rapid ventricular enlargement, large final ventricular size, decline in intraventricular pressure (IVP) and relatively low final pressure after compensation. This is the situation in newborn (CSF) infants. In contrast, with low compliance (high yield pressure), ventricular enlargement is slow, final ventricular size is relatively small, IVP remains high for long periods, and final pressure after compensation remains high. This situation obtains in older children and in adolescents, and also in fetuses, in which pressure from the uterine wall limits ventricular enlargement (Oi et al. 1990). In such cases, severe hydrocephalus with high pressure can develop with deceptively little ventricular dilatation (Jones 1987).

CSF Pulse Pressure

In addition to an increase in mean ICP, CSF pulse pressure probably plays an important role in the determination of some aspects of hydrocephalus. Flow through the aqueduct is synchronous with the systolic contraction (Marks et al. 1992). CSF pulse pressure designates the systolic–diastolic
variations in CSF pressure that result from those of arterial blood pressure transmitted by arterial wall pulsations to the CSF. The amplitude of the CSF pulse pressure varies with the mean ICP and rises sharply with increasing mean CSF pressure. Pulse pressure also depends on ventricular compliance and on the rapidity with which outflow of venous blood and CSF can compensate for the instantaneous pressure rise. CSF pulse pressure has a significant role in determination of ventricular size. An experimental three-fold increase in the pulse amplitude causes hydrocephalus in animals (Avezaat et al. 1979).

**Hydrocephalus and Secondary Pathological Changes**

Later effects of increased ICP and dilatation of the CSF spaces include the progressive development of cerebral atrophy that predominantly affects white matter and, in turn, facilitates further ventricular dilatation. There is splitting of the ependymal lining, spongy dissociation of nerve fibres and, eventually, development of astrocytosis (Da Silva 2004). The grey matter is preserved longer. Reduction of cerebral blood flow, in particular in the anterior cerebral arteries, may play a role by inducing ischaemic injury to the cerebral hemispheres (Hill and Volpe 1982).

In addition to the physical effects of pressure, oedema and distortion, there is evidence that inflammation and free radical injury may contribute to white matter injury in posthaemorrhagic hydrocephalus. High concentrations of pro-inflammatory cytokines have been demonstrated in posthaemorrhagic CSF (Sävman 2002) as have free iron and hypoxanthine both of which can generate highly reactive radicals (Bejar et al. 1983; Sävman et al. 2001). Such periventricular damage would be likely to lead to motor deficits but cognitive and sensory functions might be injured and epileptic foci initiated if the effects were more widespread in the small immature brain.

**Eventual Course of Hydrocephalus**

The eventual course of hydrocephalus will depend on the achievement of a new balance between CSF production, preservation of residual absorption capacity and development of alternative resorption pathways. If, and when, resorption and secretion of CSF equalise under a stable regime of pressure, stabilisation of hydrocephalus occurs but at the expense of a variable degree of stable ventricular dilatation.

In addition, one may observe modifications in the shape of the skull, which may expand frontally with aqueductal stenosis, whereas a fourth ventricle cyst, as in Dandy–Walker malformation, may impede caudal migration of the tentorium, which inserts on the parietal bones in an abnormally high situation. Similar mechanisms may be responsible for the skull changes that are present in hydrocephalus associated with spina bifida (Britton et al. 1988).

### EPIDEMIOLOGY OF HYDROCEPHALUS

Prevalence of congenital hydrocephalus, including cases with myelomeningocele, was 1.3–2.9 per 1000 births in 1961 (Myrianthopoulos and Kurland 1961). Over the last 50 years, congenital hydrocephalus has decreased because of folate supplementation and, in some jurisdictions, because of antenatal diagnosis and termination of pregnancy. Neonatal hydrocephalus was diagnosed in approximately 0.5 per 1000 live births in Sweden (Fernell et al. 1994).

Among preterm infants, hydrocephalus acquired postnatally from intraventricular haemorrhage (IVH) has increased several times as survival has increased. Posthaemorrhagic hydrocephalus is now the commonest type of hydrocephalus in infants with a prevalence of about 0.3 per 1000 live births in the United Kingdom. Reliable figures for the total prevalence of hydrocephalus at all ages are not available.

### CLASSIFICATION, AGE AND PRESENTATION OF HYDROCEPHALUS

The major causes of hydrocephalus vary greatly according to the age at presentation and this is shown in Table 7.2.

### Communication or Non-Communication

Clinical manifestations and treatment decisions differ considerably according to age at onset and cause. It is conventional to classify hydrocephalus according to whether there is normal communication between the ventricular system and the subarachnoid space. In non-communicating hydrocephalus, a lumbar puncture yields only a few drops of CSF; usually less than 2ml.
In communicating hydrocephalus, a lumbar puncture produces free flow of CSF. Non-communicating hydrocephalus tends to give higher ICP and a more rapid progression. However, hydrocephalus is an evolving condition which can change from non-communicating to communicating and from chronic to acute.

Fetal Hydrocephalus
Malformations are the most common causes of fetal hydrocephalus (Table 7.2). They may involve only the CSF pathways, e.g., atresia of the foramen of Monro, Chiari II malformation, membranous obstruction of fourth ventricle foramina, Dandy–Walker malformation, maldevelopment of Pacchioni granulations (exceptional), involving more extensively the brain, holoprosencephaly (especially alobar type), hydranencephaly, Walker–Warburg syndrome, and related malformations. Abnormal events during pregnancy include toxoplasmosis, intrauterine viral infections, e.g., cytomegalovirus, parvovirus B19, lymphocytic choriomeningitis, intrauterine bacterial infections, prenatal haemorrhage (intra- or periventricular), and trauma.

Infantile Hydrocephalus
Perinatal intracranial haemorrhage, especially severe intraventricular haemorrhage, bacterial meningitis, chemical meningitis (fissuring of craniopharyngioma or dermoid cyst), parasitic infections, especially cysticercosis, aneurysm of vein of Galen or other vascular anomalies, e.g., venous compression or thrombosis, mucopolysaccharidosis (Hurler syndrome), and late presentation of prenatal causes.

Childhood Hydrocephalus
Posterior fossa tumours, including periaqueductal tumours, suprasellar and sellar tumours (craniopharyngiomas, optic gliomas, pinealomas), suprasellar and incisural arachnoid cysts, and late presentation of fetal and neonatal causes.

Chiari Malformation
Chiari malformations, especially type II (Fig. 7.2; see also Chapter 6) formerly accounted for over 20% or more of cases of hydrocephalus although the frequency of this cause is now declining. Hydrocephalus associated with Chiari II malformation and myelomeningocele may develop prenatally (Chapter 1). The mechanisms of hydrocephalus are probably multiple. Descent of the brainstem results in crowding of the posterior fossa with obstruction of the fourth ventricle orifices and difficult circulation of CSF around the brainstem in the region of the foramen magnum. Prevention of hindbrain herniation is one of the reasons that supports prenatal surgery for hydrocephalus due to myelomeningocele (Adzick et al. 2011). Aqueductal stenosis is associated in one-third of cases. Alternative mechanisms may include atresia of the foramina of the fourth ventricle or ascending infection. As indicated in (Chapter 6), hydrocephalus associated with the Chiari II malformation is not infrequently accompanied by involvement.
of lower cranial nerves, and respiratory or swallowing difficulties that in some cases can be alleviated by treatment of the hydrocephalus alone. Chiari type I malformation is commonly associated with hydrocephalus in adults without myelomeningocele but with basilar osseous abnormalities (Levy et al. 1983). Such cases are rare in children.

Aqueductal Obstruction

Atresia or stenosis of the aqueduct can either be due to malformations, some of them genetically determined, or be acquired as a result of infection, haemorrhage or other mechanisms (Landrieu et al. 1979). The pathology is variable. It includes simple stenosis; forking characterised by division of the aqueduct into two or several channels, most of them ending blindly; glial membrane located at the intercollicular sulcus level, which seems to have a special relationship to neurofibromatosis type 1; and simple gliosis surrounding the stenosed aqueduct. In some cases there is wide dilatation of the upper part of the aqueduct. Such anomalies do not need to represent a primary abnormality but can be a consequence of acquired events either prenatally or after birth following IVH or bacterial meningitis.

Malformative stenosis may be associated with neighbouring anomalies such as ‘beaking’ of the collicular plate, suggesting that they may represent a mild form of dysraphism. With the use of MRI it has become clear that many cases of the so-called idiopathic aqueductal stenosis were in fact due to lesions encroaching on the aqueduct (Fig. 7.3), especially slow growing tumours of the quadrigeminal plate or periaqueductal and ‘pencil’ brainstem tumours. In a series of 71 patients with triventricular hydrocephalus (Valentini et al. 1995), MRI revealed such lesions in 15 of the 25 patients studied. A number of these tumours were associated with neurofibromatosis. None was progressive after 1–5 years follow-up, but regular examination is clearly indicated.

Genetics and Aqueductal Stenosis

Hydrocephalus may have a genetic cause (Table 7.3). L1 syndrome is the most common genetic cause of congenital aqueductal stenosis. It accounts for 5–10% of males with congenital hydrocephalus (Verhagen 2011). The L1 syndrome is caused by mutations in the neural cell adhesion molecule L1 (L1CAM) gene at Xq28. The abnormal cell adhesion molecules result in abnormal brainstem cell migration (Jouet et al. 1994; Jouet 1995). The phenotypic spectrum is variable and includes X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS), MASA (mental retardation, aphasia, spastic paraplegia and adducted thumbs) syndrome, X-linked complicated hereditary spastic paraplegia type 1 and X-linked complicated corpus callosum agenesis (Verhagen 2011). The spectrum of conditions related to mutations in this gene has been broadened to form the so-called CRASH (corpus callosum agenesis, retardation, adducted thumbs, spastic paraplegia and hydrocephalus) syndrome (Fransen et al. 1995; Silan et al. 2005). Mutation analysis of the L1CAM gene should be performed in all males with non-syndromic aqueduct stenosis. As hydrocephalus is described in about 5% of female carriers, mutation analysis of the L1CAM gene should also be considered in (mildly) affected females, especially if there is a positive family history of congenital hydrocephalus or in the presence of aqueduct stenosis of Sylvius, corpus callosum agenesis or adducted thumbs. Other types of hydrocephalus without...
Part III Neurological Consequences of Prenatal, Perinatal and Early Postnatal Interference with Brain Development

Neurological Consequences of Prenatal, Perinatal and Early Postnatal Interference with Brain Development

Aqueductal stenosis (Bickers–Adams syndrome, MASA syndrome, CRASH syndrome)

X-linked hydrocephalus without aqueductal stenosis

Non X-linked hydrocephalus

Walker–Warburg syndrome

Cobblestone complex with muscular dystrophy (COMS2, Muscle–Eye–Brain disease)

Fukuyama Congenital Dystrophy (Chapter 26)

VACTERL association

Hydrocephalus syndrome

Waaler–Aarskog syndrome

Metabolic disorders that may generate hydrocephalus (Chapter 9)

MASA, mental retardation, aphasia, shuffling gait and adducted thumbs; CRASH, corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia and hydrocephalus; VACTERL, verbal anomalies, anorectal malformations, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal/radial anomalies and limb defects.

Aqueductal stenosis may have a similar X-linked transmission (Willems et al. 1987).

Dandy–Walker Malformation

Dandy–Walker malformation is an uncommon cause of hydrocephalus, accounting for less than 2% of cases. The essential features are absence of the cerebellar vermis and enlargement of the posterior fossa. Prenatal diagnosis is possible (Fig. 7.4a). In most cases, hydrocephalus is not present at birth but develops during the first year of life (Hirsch et al. 1984). The shape of the head, with a posterior bulge, may be suggestive, but the diagnosis rests on neuroimaging (Hanigan et al. 1984) (Fig. 7.4b). The condition is not usually familial although some cases are due to chromosomal aberrations, and great care should be taken not to confuse the Dandy–Walker syndrome proper with other causes of agenesis or hypogenesis of the cerebellar vermis, which often belong to genetic syndromes (Bordarier and Aicardi 1990; see Chapter 5).

Walker–Warburg Syndrome

Walker–Warburg syndrome comprises type II lissencephaly, congenital hydrocephalus, severe neurological dysfunction from the first days of life, retinal dysplasia, microphthalmia and abnormalities of the anterior chamber of the eye. The association of eye anomalies and hydrocephalus may wrongly suggest a fetal infection but the condition is familial with a 25% recurrence risk. The presence of Peters anomaly, retinal detachment or falciform fold of the retina should always raise the possibility of this syndrome, which may also include an abnormal posterior fossa reminiscent of the Dandy–Walker syndrome (Bordarier et al. 1984).

Other Malformations and Hydrocephalus

Other malformations associated with hydrocephalus include encephaloceles, which are approximately as common as the Dandy–Walker malformation, as well as a miscellany of malformation syndromes, some of which are of chromosomal origin (Chapter 5), and some are genetically determined (Waaler and Aarskog 1980; Herva and Seppäinen 1984). Agenesis of...
the corpus callosum is often associated with marked ventricular dilatation and a large head (Chapter 3). Although virtually nothing is known about the hydrodynamics of such cases, experience indicates that many of these eventually stabilise, so that shunting should be resorted to only in the face of evident progression in patients with callosal agenesis. Agenesis of the granulations of Pacchioni and arachnoid villi is exceptional.

Not all malformations are genetically determined. It is important to realise that the same type of malformation can be due to either genetic or acquired factors, that this cannot often be determined for a particular case, and that no aetiological specificity exists. Therefore, no genetic classification is universally applicable. While it is believed that malformations tend to occur early, the lack of glial response to insults in the first half of gestation can make scar lesions acquired early in pregnancy indistinguishable from primary genetic errors. A significant proportion of cases of congenital hydrocephalus result from disorders or accidents incurred during fetal life, including infections usually of maternal origin such as toxoplasmosis, perinatal haemorrhage and congenital tumour (Fernell et al. 1994). Important causes of fetal IVH include allo-immune thrombocytopenia and inherited coagulation factor deficiency (Whitelaw et al. 1984; Povoa et al. 2007).

**DIAGNOSTIC METHODS FOR FETAL HYDROCEPHALUS**

**Ultrasonography**

Ultrasonography is the first imaging method used in diagnosis of fetal hydrocephalus (Fig. 7.5). Dilated ventricles may be recognised on routine scanning or during targeted scanning because of perceived risk such as a previous infant with a neural tube defect. Ventricular width at the level of the atria varies little between 20 and 40 weeks. Mean width is 6–7mm on each side. Based on analysis of 8216 fetuses, 10mm is 3 standard deviations above mean and has been defined as an upper limit of normal ventricular width (Almog et al. 2003). The shape of the ventricles or asymmetry of the ventricles may be a diagnostic clue.

**Magnetic Resonance Imaging**

MRI can better demonstrate the ventricular system as well as the rest of the CNS. MRI is not a routine technique as it requires either fetal immobilisation or rapid MRI techniques. It is thus indicated for cases with abnormalities detected by sonography and not clearly diagnosed by this sole investigation (Oi et al. 1998). Differential diagnosis includes agenesis of the corpus callosum with dilatation of the posterior horns, cysts of the choroid plexus and holoprosencephaly.

**Associated Anomalies**

The search for associated anomalies is of extreme diagnostic importance. A careful search for facial, limb, renal, cardiac and other intracranial abnormalities must be part of the examination. Associated abnormalities may be of grave prognostic significance. In the series of Nyberg et al. (1987) they were present in 85% of 61 fetuses with prenatal hydrocephalus, and the mortality rate for these was 66%. Similarly, associated malformations herald a poor prognosis in cases of apparently stable ventriculomegaly (Drugan et al. 1989).

When fetal hydrocephalus is suspected on sonographic examination, a complete investigation including karyotype, determination of alpha-fetoprotein and search for specific infectious agents by serology or by fetal blood sampling, has to be considered.

**OUTCOME OF FETAL VENTRICULOMEGALY**

The presence of ventriculomegaly cannot be equated with a diagnosis of hydrocephalus. Cases of isolated ventriculomegaly without other abnormalities (21 of 47 in the series of Hudgins et al. 1988) may resolve before birth and be compatible with normal development (Serlo et al. 1986). Goldstein et al. (2005) found that 26 of 34 infants in whom ventricular width at the level of the atrium was 10–15mm were normal at age 2 years. Gaglioti et al. (2005) followed 176 infants with mild (10–12mm), moderate (12.1–14.9mm) and severe (≥15mm) dilatation. The proportions of children with normal development in the three groups were respectively 93%, 75% and 62.5%. Parilla et al. (2006) found that mild prenatal ventricular dilatation disappeared in 41% of their cases, remained stable in 43%,
and progressed in only 16%. It thus appears that mild dilatation has an excellent prognosis in fetuses without detectable malformations and a normal karyotype, and often disappears as gestation progresses. Asymmetrical mild/moderate dilatation may have a similarly good outcome (Durfee et al. 2001).

OUTCOME AND MANAGEMENT OF FETAL HYDROCEPHALUS

The overall prognosis of fetal hydrocephalus (progressive ventricular dilatation) is poor. In many cases, spontaneous abortion or stillbirth results. The outcome of intraterine shunting operations is not encouraging, and most centres do not use the procedure (Bruner et al. 2006). In one series (Futagi et al. 2002), only three of 58 fetuses survived and developed reasonably. Depending on the jurisdiction, parents and clinicians may opt for termination of pregnancy for hydrocephalus of very early onset or with associated malformations and/or chromosome abnormalities (Serlo et al. 1986). In cases with a relatively thick mantle and slow progression, when parents decide to go on with pregnancy, delivery will usually be by Caesarean section. Renier et al. (1988) included in their study only patients with head circumference at birth more than 2 standard deviations above the mean. The survival rate of their 108 patients was 62% at 10 years. Only 21 of the 75 survivors had an IQ ≥80, and 16 were of borderline intelligence. Kirkinen et al. (1996) found that seven of 25 infants diagnosed during pregnancy (excluding cases with associated malformations and/or lethal syndromes) were severely disabled, and six had intermediate disability. They consider that termination should be considered if there are associated anomalies or chromosomal disorder, and if rapidly increasing ventricular dilatation is found on repeated ultrasonography.

Fetal Surgery

Prenatal repair of myelomeningocele reduced hydrocephalus impressively in a randomised clinical trial (Adzick et al. 2011); 158 women pregnant with a fetus with myelomeningocele were randomised to prenatal open closure or to postnatal closure. Only 68% of the prenatally closed infants died or required shunt surgery compared to 98% of the postnatally closed infants. Only 40% of the prenatally closed infants had shunt surgery versus 82% in the postnatally closed group. Prevention of hindbrain herniation was thought to be responsible. The downside of prenatal closure was an increased risk of death and complications from preterm delivery. However, there was a significant improvement in development at 30 months in the prenatally closed group.

HYDROCEPHALUS PRESENTING IN THE FIRST POSTNATAL YEAR

All of the causes of fetal hydrocephalus may present at birth or soon afterwards, depending on the level of fetal investigation and intervention. Important causes of postnatally acquired hydrocephalus include IVH in preterm infants (now the commonest), intracranial haemorrhage from birth trauma, postnatal infection, cysts and tumours.

Posthaemorrhagic Hydrocephalus

The term, posthaemorrhagic ventricular dilatation (PHVD) is often used by neonatologists and imagers to identify the early stages of hydrocephalus before there is excessive head enlargement. Although the ventricles are enlarged when there is atrophic loss of white matter, the term PHVD is intended to apply to CSF-driven ventricular enlargement with raised pressure. A minority (around 30% depending on definitions) of cases of PHVD are transient and do not continue to expand. The initial mechanism of PHVD is thought to be multiple blood clots obstructing the channels for re-absorption of CSF (Fig. 7.6). When older infants with posthaemorrhagic hydrocephalus came to autopsy, fibrosis of the basal cisterns and meninges together with subependymal gliosis is described (Larroche 1972) (Fig. 7.7). This can be likened to scar formation or repair gone wrong. Intraventricular injection of blood in rat pups produced PHVD in the majority and showed parenchymal and perivascular deposition of extracellular matrix proteins, probably due, in part, to upregulation of transforming growth factor beta (TGFβ) (Cherian et al. 2004). Extracellular matrix proteins such as laminin, fibronectin and vitronectin act like cement between cells and, together with TGFβ, are involved in many fibrotic diseases. Releasing ‘cement’ in and around the CSF spaces over a period of weeks is thought to be the mechanism by which re-absorption of CSF is inhibited. TGFβ 1 is stored in platelets and is thereby present in large amounts in grades 3 and 4 IVH. In addition, the rat model showed
neuromotor abnormalities weeks later, activation of microglia and periventricular white matter injury. Vinukonda et al. (2010) studied spontaneous IVH in preterm rabbits after intraperitoneal injection of glycerol. This model also shows periventricular white matter injury, inflammation and extracellular matrix proteins. Cyclooxygenase-2 inhibition was the most effective agent in preventing PHVD injury and the associated neuromotor abnormalities.

Although some preterm infants can expand their head and ventricles with very little elevation of ICP, some do elevate pressure to levels than can interfere with cerebral perfusion e.g. 150–200mmH2O (Kaiser and Whitelaw 1985) and thus injure the periventricular white matter. With the breakdown of large amounts of heme, considerable amounts of non-protein-bound iron are released into CSF and this may injure white matter through free radical generation (Sävman et al. 2001). Hypoxanthine is also released into posthaemorrhagic CSF and can injure by free radical mechanisms (Bejar et al. 1983). High concentrations of pro-inflammatory cytokines in the CSF in PHVD provide further support for inflammation being another damaging process (Sävman 2002).

Blood clot within CSF is cleared very slowly and some blood is often visible on ultrasound scans 2 months later. Fibrinolysis is relatively ineffective in CSF, probably because concentrations of plasminogen are very low and there are high concentrations of plasminogen activator inhibitor (Whitelaw et al. 1995; Hansen et al. 1997).

**Postinfectious Hydrocephalus**

**Bacterial and Fungal Ventriculitis**

Bacterial infections are an important cause of hydrocephalus as a result of adhesive arachnoiditis or granulations that may develop following the bacteriological cure of acute meningitis or in the course of a subacute or chronic meningitis, especially tuberculous meningitis. In the latter case, ventricular dilatation is often the result of both brain atrophy and increased CSF pressure. Computed tomography (CT) or MRI can show evidence of active arachnoiditis in the form of contrast enhancement of the meninges in the posterior fossa and basal cisterns (Chapter 2). Hydrocephalus may result from chemical meningitis due to fissuration of a dermoid cyst of the posterior fossa or spinal canal. The resulting arachnoiditis may also be due in part to added infection. Fungal infections include cryptococcosis and Candida meningitis, and occur especially in small preterm infants or immunosuppressed patients (Ciurea et al. 2004; see also Chapter 2). It is common for septation to occur after ventriculitis (Fig. 7.8a) resulting in localised accumulation and isolated areas of hydrocephalus (Fig. 7.8b).

**Parasitic Infections**

**Toxoplasmosis**

Intrauterine toxoplasmosis produces granulomas in the brain which often calcify. Hydrocephalus may result from aqueduct obstruction (often diagnosed antenatally) or a slower communicating hydrocephalus presenting after birth (Couvreur and Desmonts 1988) (Fig. 7.9). In exceptional cases, a late flare-up of an old periaqueductal cystic lesion has produced aqueductal stenosis in adolescents.

**Neurocysticercosis**

Neurocysticercosis in its racemose type can result in obstruction of the aqueduct or the cavities of the third and fourth ventricles or basal cisterns, thus provoking acute hydrocephalus (Cavalheiro et al. 2004).

**Viral Infections**

Viral infections are only exceptionally a cause of aqueductal stenosis. A few cases following mumps infection are on record.
Part III  Neurological Consequences of Prenatal, Perinatal and Early Postnatal Interference with Brain Development

(Ogata et al. 1992; Lahat et al. 1993), and cases of cerebellar swelling have been reported associated with varicella, with Epstein–Barr virus infection (Roulet Perez et al. 1993), with prenatal lymphocytic choriomeningitis, and with human T lymphotropic virus 1 (HTLV-1) infection (Tohyama et al. 1992).

Tumours

Tumours other than those obstructing the aqueduct are not a common cause of hydrocephalus in infants, in contrast to their high frequency in older patients. They generate hydrocephalus through variable mechanisms including blockage of CSF pathways by dissemination or compression. Congenital tumours may be associated with hydrocephalus (Chapter 14), although macrocephaly in such cases may also be due to the bulk of the tumour itself. Craniopharyngiomas and optic nerve gliomas usually manifest later. Aqueductal tumours that may be difficult to distinguish from simple aqueductal stenosis (Raffel et al. 1988) have been described above. Meningeal leukaemia or gliomatosis (Civitello et al. 1988), as well as meningeal dissemination of primary brain tumours can produce hydrocephalus through basilar obstruction or blockage of arachnoid cisterns of the convexity.

Mucopolyscaridosis

Some mucopolysaccharidoses (Chapter 9), especially Hurler syndrome, commonly cause moderate hydrocephalus associated with extreme dilatation of the Virchow–Robin spaces due to infiltration of the meninges by mucopolysaccharides.

Cysts

Cysts of the meninges and other space-occupying lesions, in contrast to tumours, are not uncommon. Posterior fossa cysts
(Di Rocco et al. 1981; Barkovich et al. 1989), paramesencephalic arachnoid cysts (Grollmus et al. 1976) and suprasellar cysts (Pierre-Kahn et al. 1990) can all produce hydrocephalus. Suprasellar cysts are often responsible, in addition, for a special endocrinological syndrome (Brauner et al. 1987). Other space-occupying lesions, (e.g. retrocerebellar subdural cyst or haematoma) can rarely cause hydrocephalus.

**Venous Mechanisms**

Obstruction within veins and sinuses or compression of these structures has long been held responsible for hydrocephalus due to deficient resorption of CSF, although experimental ligation of veins is usually well tolerated in animals. It has been postulated that an increase in sinus blood pressure can be the cause either of the syndrome of benign intracranial hypertension (or pseudotumour cerebri) or of hydrocephalus, depending on the compliance of the skull. In infants with high compliance, hydrocephalus will result, whereas pseudotumour will obtain if the brain is rigidly encased in a virtually inextensible skull. In fact, diminished compliance of the brain is essential and is probably due to increased volume of the blood compartment of the skull thus augmenting the resistance (Karahalios et al. 1996). Abnormal increases in sinus pressure may result from an anatomical obstacle or from functional factors. The former includes stenosis of the venous foramina at the base of the skull, such as occurs with achondroplasia, certain types of craniosenosis (Sainte-Rose et al. 1984), tumours compressing or invading the sinuses (Kinal 1966), and thrombosis of jugular veins or superior vena cava (Haar and Miller 1975) as a result of catheterisation (Newman et al. 1980) or surgical operations. Such cases may potentially be improved by surgically widening the basal foramina (Lundar et al. 1990).

Functional abnormalities resulting in high venous sinus pressure are mostly due to high-flow arteriovenous malformations (Chapter 15), especially of the vein of Galen, which may also act through direct compression of the aqueduct. Rarely, a more distant arteriovenous shunt, such as produced by anastomosis of the right pulmonary artery to the superior vena cava in the treatment of congenital heart disease, can produce a similar increase in intracranial venous pressure (Rosman and Shands 1978). Hydrocephalus produced by high venous pressure is generally of mild to moderate severity, although shunting has been necessary in a few cases (Haar and Miller 1975). Venous bypass between intracranial and extracranial circulations can also correct the hydrocephalus (Sainte-Rose et al. 1984), as does cure of an arteriovenous malformation.

**Hypersecretion of CSF**

Hypersecretion of CSF is observed in choroid plexus papilloma or carcinoma (Pascual-Castroviejo et al. 1983). In this case, haemorrhage from the tumour and mechanical impairment of CSF circulation from the bulk of the intraventricular mass may also play a major role in the development of hydrocephalus. The diagnosis of such lesions is easy with CT or MRI, and removal of the tumour may cure the hydrocephalus, although complementary shunting is often necessary.

**DIAGNOSIS OF HYDROCEPHALUS**

Accelerated head growth is the major and most striking manifestation. After a diagnosis of IVH, significant traumatic haemorrhage or any infection of the brain, it is important to regularly measure the occipito-frontal head circumstances but ventricular enlargement can precede excessive head enlargement by 7–14 days. Between 24 and 32 weeks’ gestation, average head enlargement is about 1mm per day but from 32 to 40 weeks the growth velocity is less, being around 0.7mm per day (Fenton 2003). Excessive head enlargement can be defined as 2mm or more per day. Head circumference that crosses two centile lines is also suspicious even if not averaging 2mm per day.

The anterior fontanelle is usually large and tense or full in the sitting position. Splaying of the sutures of the cranial vault may be palpable. The scalp may appear abnormally thin and its veins dilated, strikingly so when the infant cries. This dilatation is the result of diversion of the intracranial venous drainage through emissary veins as a result of increased venous sinus pressure (Sainte-Rose et al. 1984).

Ocular manifestations are useful for the diagnosis. The ‘setting sun’ phenomenon is a downward conjugate deviation of gaze such that the iris is partially covered by the lower lid while the sclera is exposed above the upper rim of the iris. The latter is due in part to retraction of the upper eyelid. The mechanism of the setting sun phenomenon is probably compression of the mesencephalic tectum, but it is not specific for hydrocephalus as it has been observed in children with subdural haematomas (Fig. 7.10). Moreover, retraction of the upper eyelids is occasionally present in otherwise normal infants at rest and can be regularly induced in neonates by sudden change from a vertical to a supine horizontal position or by removal of a bright light that had been placed in front of the eyes (Cernerud 1975). External strabismus is common and may be related to involvement of the optic radiations or VIth nerve paralysis. Optic atrophy is found in advanced cases, but papilloedema is rare unless the hydrocephalus is evolving rapidly such as occurs with papilloma of the choroid plexus (Pascual-Castroviejo et al. 1983). Seizures were observed in almost half the cases of Noetzel and Blake (1992) but were more related to parenchymal brain pathology than raised ICP. In most infants, functional symptoms are not obvious and enlargement of the head is the major feature (49% of cases in the series of Kirkpatrick et al. 1989). That series also points to the rare occurrence of atypical features such as profuse sweating, neurogenic pulmonary oedema and stridor. An interesting presentation is the ‘bobble-head doll’ syndrome, which is caused by dilatation of the third ventricle or by suprasellar cysts and consists of 2–3Hz oscillatory movements of the head, usually in association with developmental delay. A slow tremor in patients with...
hydrocephalus has been regarded as a possible equivalent of the ‘bobble-head doll’ phenomenon (Bhattacharyya et al. 2003).

NEUROIMAGING AND ANCILLARY INVESTIGATIONS FOR HYDROCEPHALUS IN INFANTS

ULTRASOUND

Ultrasonographic examination through the anterior fontanelle is safe and simple as long as the fontanelle is open. It is particularly well suited for repeated follow-up examinations. Quantitative criteria for diagnosis of PHVD have been widely used in Europe. The most commonly used measurement is the ventricular index of Levene (1981) measured in the mid-coronal view; it is the dimension from midline to the lateral border of the lateral ventricle (Fig. 7.11). In a survey of 30 European neonatal units in 17 countries, Brouwer found that 13 centres used the 97th centile of Levene to diagnose PHVD and nine used 4mm over the 97th centile (Brouwer et al. 2012). Davies et al. (2000) added the anterior horn width (to represent ballooning of the lateral ventricle), third ventricle width and thalamo-occipital distance (Fig. 7.12). In several therapeutic trials of PHVD, ventricular index (width) 4mm over the 97th centile on each side was an inclusion criterion. In the most recent trial, ventricular index over the 97th centile (Fig. 7.13) and anterior horn width 6mm on each side were used as criteria.

COMPUTED TOMOGRAPHY

CT allows for assessment of ventricular dilatation and for some rough quantification: measurement of the ventricular surface and of the ventricular surface index (ventricular surface/total surface on the same cut), and of Evan’s index (distance between the lateral walls of left and right ventricles/total width of brain). Evans’ index over 0.3 is considered excessive. CT also shows the parenchyma, and the presence of periventricular hypodensities, especially around the anterior and, to a lesser extent, the posterior horns, may indicate transependymal CSF absorption and evidence of raised CSF pressure (Fig. 7.14). Because of the significant radiation exposure involved, CT is usually only used in infants for emergency diagnosis of haemorrhage.

MAGNETIC RESONANCE IMAGING

MRI can give much more information without radiation and has supplanted CT except for emergencies. The possibility of obtaining multiplanar cuts allows for a detailed study of intracranial anatomy (Britton et al. 1988). Transependymal resorption is shown as areas of low T1 and intense T2 signal (Fig. 7.15), and the status of myelination can be assessed. MRI can permit measurement of CSF volume in the various compartments of the CNS (Condon et al. 1986; Brunelle 2004).

CSF flow can be demonstrated using specially designed sequences. Aqueductal CSF flow can be seen in the foramina of Monro, fourth ventricle and aqueduct of Sylvius (Nitz et al. 1992). In the aqueduct, downward flow can clearly be seen to be synchronous with the cardiac systole and reversed upward flow with diastole, illustrating the importance of arterial pulsations in CSF circulation. Semi-quantitative methods are being developed (Brunelle 2004). They are also used to assess the functioning of therapeutic ventriculocisternostomies.

MEASUREMENT OF CSF PRESSURE

CSF pressure cannot be measured transcutaneously with sufficient accuracy for clinical decision-making. Invasive measurement requires an intracranial catheter or needle but if there is ventriculo-spinal communication and horizontal posture, lumbar puncture pressure is equivalent. In children, normal pressure when reclining is 50–120mmH2O at the level of the foramen of Monro. In the standing position it becomes negative (average ~50mmH2O). It fluctuates during the sleep–waking cycle, with plateau waves of about 100mmH2O every 50–75 minutes during rapid eye movement sleep, and it appears that high plateau waves even with a normal resting pressure...
indicate that hydrocephalus is not arrested (Allen 1986). In newborn and preterm infants within the first 3 months, normal CSF pressure is about 40mmH₂O with an upper limit of about 8mmH₂O (Kaiser and Whitelaw 1986). Infants with expanding PHVD had a mean pressure of 12mmH₂O but with a wide range (Kaiser and Whitelaw 1985).

**Doppler cerebral blood flow velocity**

Modern ultrasound equipment includes pulsed Doppler enabling velocity measurement. As ICP rises, Doppler cerebral blood flow velocity (CBFV) tends to decrease as any rise in blood pressure (Cushing response) is usually insufficient to maintain cerebral perfusion pressure (Kaiser and Whitelaw 1988). The resistance index, which is calculated...
from systolic velocity minus diastolic velocity divided by systolic velocity, has the great advantage over absolute velocity measurement in metre/second in that resistance index is independent of the angle at which the ultrasound beam meets the artery. Resistance index that progressively increases to over 0.85 is suggestive of rising ICP and loss of end-diastolic flow velocity indicates impaired cerebral perfusion (Fig. 7.16). Thus it is useful to record Doppler resistance index whenever a cranial ultrasound scan is being carried out to assess ventricular enlargement or raised ICP.

**Electroencephalography**

Electroencephalography (EEG) is increasingly used in neonatal intensive care, often as amplitude-integrated EEG (aEEG). Repeated EEG may show a deterioration with increasing discontinuity as ventricular dilatation increases in preterm infants with PHVD and this may precede other signs of raised ICP. Such changes reversed after ventricular drainage (Klebermass-Schrehof et al. 2013). Somatosensory evoked potentials show increased latency in infants with PHVD as CSF pressure increased and improved when treatment lowered pressure (de Vries et al. 1990).

**PROGNOSIS OF UNCOMPPLICATED HYDROCEPHALUS**

Eighty survivors of ‘pure’ hydrocephalus operated between 1956 and 1976 in Cleveland were reviewed by Nulsen and Rekate (1982). These were infants not complicated by primary brain disease, haemorrhage or spina bifida. Of these 43 had aqueduct stenosis, 13 had blockage at the outlets of the fourth ventricle and 24 had communicating hydrocephalus. There was a good correlation between IQ and the thickness of the frontal cerebral mantle (determined at follow-up). Normally the cerebral mantle is 5.0–5.5cm. The children with a cerebral mantle of 3.0cm or more had an IQ distribution approaching normal. All eight patients failing to achieve a cerebral mantle of 2.0cm were not adequately shunt-operated until after 6 months of age. Six children with a final mantle of 2.0–3.0cm (IQ 63–95) were all adequately shunted after 5 months. All children adequately shunted before 5 months had a mantle measurement over 3.0cm, including nine children with initial mantle thickness of less than 1.0cm. No increase in mantle size occurred in any of the children first operated after age 18 months. The authors concluded that if infantile hydrocephalus is severe with a frontal mantle of less than 2.0cm, the opportunity for good development diminishes with time. The benefit of early shunting in severe hydrocephalus is supported by experimental work. Rat pups with inherited hydrocephalus were shunted at 4–5 days or 10–11 days. Early shunting greatly reduced neural injury in the visual cortex (Boillat et al. 1997).

**PROGNOSIS OF HYDROCEPHALUS WITH MYELOMENINGOCELE**

The relationship between frontal cerebral mantle thickness and IQ is much less predictable than in ‘pure’ hydrocephalus. These infants are identified at birth because of the myelomeningocele and hydrocephalus is expected. Very few are operated on late because of delayed diagnosis. Thus it is relatively unusual to fail to develop at least a 3cm-thick frontal mantle. The IQ distribution of the Cleveland series of hydrocephalus with spina bifida was much lower than for children.
with ‘pure’ hydrocephalus and a 3.0cm mantle (Nulsen and Rekate 1982). Over 50% had IQ below 80 versus 15% and only 15% were above 100 (versus 51%). The frequency of CSF infections in this group may have had an adverse effect on development.

Recent cognitive outcomes are considerably better. In the randomised trial of prenatal closure of meningocele, only 33% of the postnatally closed infants had a 30 month Bayley Mental Development Index (Bayley MDI) below 85. Only 26% of the prenatally closed infants had an MDI below 85 (Adzick et al. 2011).

**PROGNOSIS OF POSTHAEMORRHAGIC HYDROCEPHALUS**

The Ventriculomegaly Trial (1994) and PHVD drug trial (Kennedy et al. 2001) used ventricular index 4mm above the 97th centile as entry criterion and had standardised developmental assessment. If there were no parenchymal lesions seen on ultrasound, the incidence of cerebral palsy (CP) was approximately 40% and about 25% had multiple impairments. If parenchymal echodensity or lucency was seen, in addition to PHVD, cerebral palsy was found in 80–90%. A large recent study of 998 infants with birthweight below 1000g showed that, in infants with grade 3 IVH, the subsequent need for shunt surgery greatly increased the rate of cerebral palsy and cognitive disability. In grade 4 IVH, the need for a shunt also increased disability with 48% having Bayley MDI below 50 and 80% having cerebral palsy (Adams-Chapman et al. 2008).

Recently, we have investigated quantitative imaging in PHVD. The area of a parenchymal infarction measured in the parasagittal ultrasound view has a negative linear correlation with motor developmental quotient (DQ) at 2 years corrected age (Jary et al. 2012a). Lateral ventricular area in the coronal view at the start of treatment did not correlate with development at 2 years. Infants with PHVD who subsequently required shunt surgery had larger intraventricular clot area at the start of treatment. On MRI at term in 25 infants with PHVD, total cerebral volume, thalamic volume and cerebellar volume correlated positively with motor DQ at 2 years (Jary et al. 2012b). Some of the infants showed very significant brain growth impairment with the cerebellum being less than 50% of expected size (Fig. 7.17).

**TREATMENT OF HYDROCEPHALUS IN INFANTS**

The decision to treat hydrocephalus depends on the answers to three questions:

1. Is ICP increased?
2. Is there active expansion of the ventricular CSF?
3. Is the infant symptomatic from raised ICP?

**Figure 7.17** Cerebellar volume measured on MRI correlated with motor developmental quotient at 2 years in infants with posthaemorrhagic ventricular dilatation (PHVD) \( (r = 0.6, p = 0.0002) \).

The method of initial treatment depends on two questions:

1. Is the ventricular enlargement permanent or might it be transient?
2. Are there technical factors that make a ventriculoperitoneal shunt operation technically difficult or at very high risk of complications?

**MEDICAL TREATMENT OF POSTHAEMORRHAGIC VENTRICULAR DILATATION**

In preterm infants with PHVD, immediate ventriculoperitoneal shunt surgery is contraindicated because of the very high blood and protein content of CSF and because the tiny infant is at high risk for skin breakdown, infection, and respiratory complications. Furthermore it is difficult, when ventricular dilatation starts, to know if the process will be permanent or transient. Thus a variety of temporary strategies have been used to control pressure and ventricular size.

Repeated lumbar or ventricular taps have been tested in four randomised trials without any evidence of reducing shunt surgery or disability (Whitelaw 2001a). Acetazolamide and frusemide reduce CSF production but, when tested in randomised trials, the infants in the drug group had worse outcome than the comparison group (Whitelaw et al. 2001b). Isosorbide reduces CSF production by an osmotic effect but a high incidence of side effects such as vomiting has been reported and no randomised trial has been carried out (Liptak et al. 1992).

Intraventricular injection of a fibrinolytic agent was suggested as it has improved outcome in coronary artery thrombosis and a local dose insufficient to produce a systemic effect could be given. Experience in infants with PHVD has been inconsistent and two small trials of intraventricular streptokinase showed no evidence of benefit (Whitelaw 2007a).

External ventricular drain and repeated tapping of a ventricular reservoir have their advocates but no results of
randomised trials have been published. However, a non-randomised Dutch retrospective study of 144 infants with PHVD found that those whose treatment had started with ventricular index over the 97th centile had better DQ at 2 years than those whose treatment started after ventricular index had increased above 4mm over 97th centile (de Vries et al. 2002). Third ventriculostomy and choroid plexus coagulation have had very limited use in PHVD.

In view of the poor prognosis of PHVD and the lack of a safe and effective treatment, our Bristol group developed a new approach aimed at removing as much as possible of the free iron, inflammatory cytokines and old blood as well as gently reducing pressure and distortion earlier than would occur with lumbar puncture (Whitelaw et al. 2007b). Right frontal and left occipital ventricular catheters were inserted. A small dose (0.5mg/kg) of tissue plasminogen activator was injected into the ventricles and left for 8 hours. The occipital catheter was then connected to a sterile closed system and the height of the reservoir was adjusted to maintain ICP below 90mmH 2O. Artificial CSF (containing gentamicin and vancomycin) was pumped in via the frontal catheter at 20ml per hour. The drainage fluid usually started looking like cola and gradually cleared to look like white wine, at which time irrigation stopped and the ventricular catheters were removed, usually 3–7 days after the start.

Drainage irrigation and fibrinolytic therapy (DRIFT) has been tested in a randomised trial involving 77 infants with PHVD in four centres, 39 receiving DRIFT and 38 receiving conventional treatment with lumbar puncture followed by tapping a reservoir. The trial was stopped early because of an excess of secondary IVH in the DRIFT group and there was no difference in shunt surgery between the two groups (Whitelaw et al. 2007b). However, developmental assessment at 2 years corrected age showed severe cognitive disability (Bayley MDI <55) was significantly reduced with DRIFT (Whitelaw et al. 2010). Median Bayley MDI was improved by more than 18 points in the DRIFT group. Importantly, the infants in the DRIFT group who had secondary IVH did not have more disability than those who did not bleed. These children have had extensive testing at age 10 years and significantly more of those who had received DRIFT have survived with normal cognition. The DRIFT trial is the only trial to demonstrate any benefit from any intervention in PHVD.

SURGICAL TREATMENT

Surgical treatment of hydrocephalus has been radically modified by the introduction of extracranial shunting procedures. A striking evolution has been the development of alternative treatments to shunts, especially endoscopic procedures that are now preferred whenever possible to shunts because of the many problems these pose. Although shunts are still the more common form of treatment they are no longer the first surgical possibility to consider in many cases. Treatment of the cause of hydrocephalus, alternative types of diversion are also to be discussed before considering shunts. There is some indication that internal diversions such as ventriculocisternostomy might be effective even for postmeningitis or posthaemorrhagic cases.

Medical treatment is rarely considered except in slowly progressive hydrocephalus and in the specific case of posthaemorrhagic hydrocephalus in preterm infants (see Posthaemorrhagic Hydrocephalus section above).

As discussed previously, the decision to operate on a patient with hydrocephalus may not be easy because ‘arrested hydrocephalus’, or ‘compensated hydrocephalus’, even though it is rare, does exist and because complications of treatment are far from negligible. It seems reasonable to defer operation in children over 3 years of age with apparently arrested hydrocephalus when intellectual performance is within normal limits and seems stable (McLone and Aronyk 1993). In younger children, the trend is to place a shunt because of the danger to normal development posed by persistent hydrocephalus.

The decision for surgical treatment may also be difficult in patients with long-standing hydrocephalus, spastic diplegia and neurodevelopmental problems. The degree of reversibility of such abnormalities is not known. On the other hand, insidious deterioration certainly occurs in many cases, and surgical treatment is indicated whenever there is doubt about the progression of the disorder.

Treatment of the Cause

This applies to hydrocephalus secondary to space-occupying processes. Removal of a brain tumour will re-establish a normal CSF circulation. However, postoperative haemorrhage and aseptic meningitis may lead to the development of adhesions that will maintain active hydrocephalus. Although some neurosurgeons advise shunting preliminary to tumour removal, the majority prefer to shunt only postoperatively when necessary. Excision or shunting of an arachnoid cyst is also a form of aetiological treatment but will be considered with shunting techniques.

Surgical treatment over the last three decades has been mainly by CSF diversion by shunts. More recently, however, major improvements in surgical techniques and the realisation that shunts were the source of multiple and often severe complications that might occur many years after surgery (see Shunting Operations section) has led to an increased use of internal diversion techniques especially ventriculocisternostomy, which tends now to be regarded as the intervention of choice whenever it is possible.

Ventriculocisternostomy

Any form of hydrocephalus that is purely obstructive in nature, with one of multiple sites of obstruction located between the third ventricle and the peripontine cistern, can be cured by endoscopic third ventriculostomy (Cinalli 2004).
The main types amenable to ventriculocisternostomy are indicated below.

Primary aqueductal stenosis due to forking, glial stenosis, membrane or other congenital anomaly is the best candidate for the operation. A satisfactory circulation of CSF can be restored by establishing a patent communication between the anterior recess of the third ventricle and the chiasmatic cistern, as the CSF pathways below the aqueduct are patent. The operation consists in perforating the floor of the third ventricle anterior to the mamillary bodies under endoscopic control.

Tumoural hydrocephalus is also amenable to ventriculocisternostomy in some tectal gliomas and in pineal tumours (Ferrer et al. 1997; Mizoguchi et al. 2000; Pople et al. 2001). It is also used as a preoperative prevention of postoperative hydrocephalus in tumours of the posterior fossa (Sainte-Rose et al. 2001).

Hydrocephalus of other causes in which ventriculostomy has been used include obstructive tetraventricular hydrocephalus due to obstruction of the fourth ventricle foramina (Cinalli 2004), some cases of vein of Galen malformation, and cases of postinfectious aqueductal stenosis due to toxoplasmosis and mumps encephalomyelitis. Some investigators have used it as a first therapeutic attempt in cases of posthaemorrhagic hydrocephalus, when it is not indicated in principle because of the possibility of basal cistern blockage, and found it effective in a significant proportion of cases.

Cysts associated with hydrocephalus, especially suprasellar cysts (Pierre-Kahn et al. 1990; see Chapter 14) and incisural cysts, can be treated by ventriculocystostomy, a procedure similar in its principle to ventriculocisternostomy whereby a communication is established between the third ventricle and the cysts. In such cases, the operation may avoid a pressure dysequilibrium between the ventricular system and the cyst that can be responsible for postoperative dilatation of either cavity.

Hydrocephalus in shunt malfunction has also been treated by ventriculostomy, when feasible (Punt 2004), and was successful in 23 of 30 patients in one series (Cinalli et al. 1998) allowing control without shunt.

The success rate of ventriculostomy reported in the literature ranges widely because it essentially depends on the patient selection criteria, with a mean of 68% (Cinalli 2004). The variable results are mainly due to the heterogeneity of the operated cases. If only triventricular hydrocephalus cases are considered, the average success rate is above 60%. Venticulocisternostomy is effective in reducing intracranial hypertension but usually leaves a persistent dilatation of the ventricles (Hirsch 1982; Cinalli 2004). The decrease in ventricular size is less than with shunting operations. Volume reduction of the order of 30–50% is expected unless there is parenchymal atrophy in long-standing cases. This less marked decrease avoids the problem sometimes seen of ventricular collapse with post-shunt pericerebral collections in patients with a large skull. Symptoms and signs of intracranial hypertension disappear promptly, and ICP should return to normal within 10 days. In case of persistence, shunting becomes necessary.

Complications of ventriculostomy include intraoperative complications such as bradycardia, asystole and haemorrhage, and also damage to the fornices that usually has minimal consequences. Hypothalamic damage may produce severe consequences (Teo 2004). Vascular damage to the basilar artery can be life threatening but is rare. Failure to control the hydrocephalus is frequent in young infants. Most of these complications should be avoided by correct technique (Navarro et al. 2006). However, the success rate decreased with increasing age to less than 50%, even when taking into account aetiology (Koch-Wiewrodt and Wagner 2006). Late failure of the ventriculostomy does occur, sometimes years after the procedure. It may result from glial scarring stenosing or obstructing the orifice but may also occur in the face of an open stoma. This is a dangerous complication that may result in acute midbrain syndrome. Therefore, patients should be informed and followed closely. Failure of the ventriculostomy seems not to occur after the 5 years following operation (Cinalli 2004).

**Shunting Operations**

These techniques aim at diverting the CSF that cannot reach its normal areas of resorption toward another site of drainage. This is achieved by inserting a unidirectional valve system with a specified level of opening pressure between a proximal catheter placed in the ventricular system (or other fluid-containing cavity) and a distal catheter that carries the outflow of the valve to the draining site.

Under special circumstances, for instance when there is infection of the CSF or the fluid is haemorrhagic and might obstruct the system, the distal catheter may be temporarily drained into a sterile pouch, external to the patient. External drainage is limited by the risk of infection and the consequent necessity to maintain the patient in strict aseptic conditions.

Internal shunts have become the standard treatment in the vast majority of cases of hydrocephalus. Numerous catheters and valve systems are available with different mechanisms and hydrodynamic characteristics. Residual ICP after shunting will depend on the opening pressure of the valve or the pressure within the drainage cavity and on the resistance of the shunt. Available valves are classified into low-pressure (opening pressure 20–50mmH₂O), mid-pressure (50–80mmH₂O) and high-pressure valves (80–120mmH₂O). The flow, once the valve is open, will be determined by the ratio of the differential pressure between the two extremities of the system to its resistance. Most systems have a constant resistance so that the standing position inevitably produces overdrainage. Over the years many attempts have been proposed to overcome this complication, namely ‘externally adjustable opening pressure shunts’, ‘anti-gravity devices’, ‘antisiphon devices’ and various combination of these shunt adjuncts. Variable resistance systems have been proposed (reviewed by Sainte-Rose et al. 1987) in order to avoid such problems.
Currently, drainage is generally into the peritoneal cavity (ventriculoperitoneal shunt), because this form of shunt is easier to insert and does not need lengthening with growth of the patient since a considerable length of catheter may be left within the peritoneum without serious problems (Vinchon and Dhellemmes 2004). Ventriculoperitoneal shunts are now used only when the peritoneum does not absorb enough fluid or in cases of peritoneal or intraperitoneal infection.

Most systems include an inbuilt reservoir, placed subcutaneously over the skull, which theoretically allows shunt functioning to be assessed by pumping the reservoir. In fact, the correlation between response to pumping and functioning of the shunt is poor. According to Piatt (1992) only 18–20% of blocked shunts cannot be pumped, and the ability to pump indicates shunt patency in only 65–81% of cases. There is thus no simple manoeuvre for assessing shunt functioning. For this reason, some surgeons always use a separate fluid reservoir for pressure measurement and fluid collection (Leggate et al. 1988).

Lumboperitoneal and other shunts are now only rarely used. Some surgeons employ them for the treatment of pseudotumour cerebri. The catheter is introduced into the lumbar subarachnoid space and anchored to the lumbar fascia. The tube is then fed through a subcutaneous tunnel to exit through a small incision in the loin. Then, with or without interposition of a valve, the catheter is fed into another subcutaneous tunnel to the paraumbilical area where it is introduced into the peritoneal cavity as a ventriculoperitoneal catheter.

In spite of considerable progress in the development and techniques of use of CSF shunts, numerous complications can and do occur (Hirsch and Hoppe-Hirsch 1988; Sainte-Rose et al. 1989; Di Rocco et al. 1994). They are more common in infancy and following operation for aqueductal stenosis (Di Rocco et al. 1994). Table 7.4 lists the main complications of shunts. The major complications are infection and shunt failure, and associated incidents such as fracture and migration of catheters.

Infection remains a serious complication of shunt procedures. Its incidence varies between 4% and 8% in published series (Renier et al. 1984; Ammirati and Raimondi 1987; Hirsch and Hoppe-Hirsch 1988; Di Rocco et al. 1994) but the lower figure now seems to be generally accepted. The rate is higher in infants under 6 months of age. The infecting organism is Staphylococcus epidermidis in half the cases, S. aureus in a quarter, and Gram-negative organisms in about a fifth (Bayston 1994). Rare pathogens may colonise shunts (see Chapter 11). Infection is usually an early complication but can occur months or years after operation. Meningitis is the dominant infection (almost two-thirds of cases), while peritonitis occurs in about 20% and wound infection in over 10%. The clinical picture is often insidious, especially when S. epidermidis is the cause, and the diagnosis may be difficult, especially when eosinophilia is the prominent CSF anomaly (Vinchon et al. 1992). Death is possible, especially with Gram-negative meningitis. Localised peritoneal infection can lead to ulceration of the bowel with exteriorisation of the catheter through the anus. Septicaemia has become rare since ventriculostrial shunt is now uncommon. The same applies to shunt nephritis (Wald and McLaun 1978) and to cor pulmonale (Sleigh et al. 1993).

Prevention of infection by strict aseptic measures is essential (Hirsch and Hoppe-Hirsch 1988). Prophylactic antibiotics seem to reduce shunt infections and should be given on the day of operation and the following day. Treatment of established infection includes aggressive antibiotic therapy for 10–20 days on average after removal of the shunt. The shunt is reinserted when CSF cultures are sterile and CSF glucose back to normal. Some authors advocate initial antibiotic treatment for 5–6 days before removal, and immediate replacement of the shunt. Antibiotics are then continued for 2–3 weeks (Hirsch and Hoppe-Hirsch 1988). In an occasional case antibiotic treatment with injections into the shunt may sterilise

### Table 7.4 Main complications of ventricular shunts

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
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<tr>
<td><strong>Infection</strong></td>
<td>Septicaemia (only with ventriculostrial shunts)</td>
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<tr>
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<td>Meningitis</td>
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<td>Peritonitis</td>
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<td></td>
<td>Shunt nephritis (only with ventriculostrial shunts)</td>
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<td></td>
<td>Wound infection</td>
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<td><strong>Primary misplacement</strong></td>
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<td>Intra-abdominal</td>
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<td>Intravascular</td>
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<td></td>
<td>Puncture porencephaly</td>
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<tr>
<td><strong>Blockage and underdrainage</strong></td>
<td>Proximal obstruction of choroid plexus, brain tissue, meninges, ependyma</td>
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<td></td>
<td>pathological tissue or foreign material</td>
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<td></td>
<td>Distal obstruction of abdominal or atrial catheter; development of intra-abdominal cyst; cerebrospinal fluid ascites</td>
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<tr>
<td><strong>Fractures of catheter or connectors</strong></td>
<td>In hollow viscera (intestine, bladder, stomach)</td>
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<td>In inguinal canal with hydrocele; coiling around intestine with intestinal obstruction</td>
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<td>Isolated ventricles – especially trapped fourth ventricles with secondary stenosis of the sylvian aqueduct</td>
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<tr>
<td><strong>Migration of catheter</strong></td>
<td>In hollow viscera (intestine, bladder, stomach)</td>
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<td>In inguinal canal with hydrocele; coiling around intestine with intestinal obstruction</td>
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<td>Isolated ventricles – especially trapped fourth ventricles with secondary stenosis of the sylvian aqueduct</td>
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<td><strong>Overdrainage</strong></td>
<td>Intraocular hypotension</td>
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<td>Shunt dependency</td>
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<td>Post-shunt pericerebral collections</td>
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<td><strong>Underdrainage</strong></td>
<td>Slit ventricle syndrome</td>
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<td>Post-shunt craniosynostosis</td>
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<td>Stenosis of the spinal canal</td>
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<td><strong>Epilepsy</strong></td>
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the CSF (Bayston 1994). Removal of the shunt seems to give the lowest mortality. On the other hand, the incidental occurrence of Haemophilus influenzae meningitis in a shunted child can often be successfully treated without removing the shunt (Rennels and Wald 1980). Peritonitis is usually cured by antibiotic therapy and removal of the infected catheter. Surgery is rarely necessary. Low-grade infection with formation of intraperitoneal cysts can be detected with the help of sonography.

Shunt failure can result from primary misplacement of the shunt. In such cases, parenchymal haemorrhage, traumatic puncture of the internal capsule or puncture porencephaly can be responsible for hemiplegic sequelae (Bolsthauser et al. 1980).

Most commonly, shunt failure occurs in correctly placed shunts. In the series of Sainte-Rose et al. (1989), 81% of 1620 shunts had failed by 12 years after insertion. The risk of failure was highest, at 30%, in the first postoperative year. Disappointingly, the risk was 7–14% for each subsequent year and there was no indication of a trend toward improvement with time. Blockage of the shunt was the cause of failure in half the cases, most frequently at the ventricular end. Fracture, migration and disconnection were next in frequency, being observed in 14% of cases.

Migration of catheters following rupture of connectors may be particularly difficult to diagnose as CSF often continues to flow along the subcutaneous fibrous tunnel for prolonged periods. Cortical visual impairment is a complication of shunt dysfunction. It is probably due to compression of the posterior cerebral arteries by the tentorium, when there is a sudden increase of ventricular size with resultant downward displacement of the brain. CT shows bilateral occipital infarcts (Arroyo et al. 1985).

Sainte-Rose et al. (1989) reported a mortality related to shunt failures of 1%, and the incidence of subsequent epilepsy and of recurrent shunt failure was significantly increased. The symptoms and signs of obstruction may be overt or insidious. Parents should be advised to report immediately bouts of headaches or vomiting, lethargy, or the development of diplopia or other neurological signs. In other patients, only vague symptoms and behavioural changes are present such as decreased spontaneity or poor school performance, perhaps in association with mild headaches. Still other children have intermittent shunt obstruction. Sudden death can occur (Hayden et al. 1983); hence the need for rapid hospitalisation. Non-functioning shunts need not be symptomatic. In the experience of Hayden et al., 23% of 307 patients with nonfunctional shunts remained asymptomatic for an average of 27 months.

It seems that about 85% of shunted patients will have to keep a shunt in place indefinitely if no complications supervene, and there is no simple means of determining in which patients the shunt can be removed despite various techniques having been proposed (Hayden et al. 1983). The diagnosis of blocked shunt is often difficult, and various techniques of assessment have been proposed, such as measurement of the Doppler pulsatility index (Pople et al. 1991) and MRI flow study (Frank et al. 1990). Watkins et al. (1994) showed that a normal CT does not exclude blockage; percutaneous manometry in 26 cases gave no false positives or negatives but the results were equivocal in five children. In fact, all shunts are bound to stop functioning with time, as the annual rate of failure remains constant over the years (Sainte-Rose et al. 1991). This is due mostly to fibrous changes and calcification around the catheters. However, the diagnosis of non-functioning shunt is quite difficult and no method of recognition is consistently successful. This gives rise to discussions about removal of uncomplicated but probably nonfunctional shunts. There is no reason to remove a shunt in asymptomatic patients, even if it is thought to be nonfunctional, as this can result in intracranial hypertension.

It is hoped that the development of new material can lead to prevention of the formation of biofilms and may reduce inflammatory or other tissue reactions, thus avoiding the two most common shunt complications, failure and calcification.

Overdrainage is a frequent complication of ventriculo-peritoneal shunts because of the ‘siphon effect’ that occurs in the upright position, due to the height of the hydrostatic column between the inlet and the outlet of the shunt. In standing patients, the draining capacity of the shunt exceeds the ventricular CSF secretion rate and overdrainage is constant. Overdrainage is more important with low-resistance valves (spring-ball type or silicone rubber diaphragm type) than with high-resistance valves (silicone rubber slit types).

Complications of overdrainage classically include subdural effusions, slit ventricle syndrome, orthostatic CSF hypotension, craniosynostosis (Serlo et al. 1985; Epstein et al. 1988). Overdrainage is also an important factor in the mechanism of trapped ventricles. A trapped fourth ventricle can behave as any space-occupying posterior fossa lesion and requires placement of an additional shunt within the cavity. The diagnosis by neuroimaging is straightforward. But above all chronic overdrainage is the major cause of ‘late’ shunt proximal obstruction as it will favour the migration into the drainage system of various tissue or debris (choroid plexus, ependymal or glial tissue).

Intracranial hypotension occurs especially after lumbo-peritoneal shunts (Rando and Fishman 1992) and can be responsible for headaches, vertigo and vomiting. MRI may show striking dural enhancement with gadolinium (Fishman and Dillon 1993; Pannullo et al. 1993; Mokri et al. 1995). The same phenomenon has also been reported following lumbar puncture (Krause et al. 1997). In rare cases, prolonged hypotension may result in spinal canal stenosis (Kobayashi and Hashi 1983). Overdrainage is also one of the causal factors of isolated ventricles (Matsumoto and Oi 1985) and may be associated with an increased incidence of epilepsy.

Slit-like ventricles are seen in about 20% of cases but most remain asymptomatic. The ‘slit ventricle syndrome’ is characterised by recurrent signs of increased ICP, due to intermittent obstruction of the shunt by the walls of the ventricle. It may also manifest as chronic headache. CT shows only slightly larger ventricles in the presence of shunt obstruction than
with a functioning shunt. This is because the slit ventricles are also usually stiff ventricles, in part because of the loss of CSF volumetric buffering reserve, necessary for instance in the case of vasodilatation, and in part because of periventricular gliosis as a result of previous infections and gliosis impairing re-expansion of previously collapsed ventricles. Prevention of the slit ventricle syndrome is difficult (Rekate 2004). Various techniques have been proposed such as antisiphon valves or constant flow valves (Sainte-Rose et al. 1987).

Post-shunt pericerebral collections occur in about 3% of shunted patients but are symptomatic in only half the cases (Hoppe-Hirsch et al. 1987). A simple treatment is insertion of a valveless shunt into the subdural cavity draining it to the peritoneum in order to establish a temporary lower pressure in the subdural space than in the ventricle.

Orthostatic CSF hypotension and shunt dependency are often associated with the presence of slit ventricles. They can be associated with headaches or behavioural changes but are more commonly asymptomatic.

Post-shunt craniosynostosis is in most cases limited to the premature fusion of the sagittal suture with resulting scaphocephaly. Only exceptionally do post-shunt synostoses represent more than a purely cosmetic problem, requiring surgical correction.

Epilepsy has been reported to be more common in shunted patients than in unoperated ones. The reported occurrence varies enormously in different series that are extremely heterogeneous and impossible to compare. Ines and Markand (1977) found the frequency of seizures to be 18.2% before operation and 65.4% after. In a study of 171 patients, Di Rocco et al. (1985) found that 34 (19.9%) had seizures, 25 of these having had seizures before surgery. Saukkonen et al. (1990) reported that 48% of their 168 shunt-treated patients had seizures, regardless of the aetiology of hydrocephalus. They were of the opinion that the mere presence of a shunt device in the brain parenchyma is of relatively little importance. Infections and parenchymal damage due to the cause of hydrocephalus were associated with an increased seizure rate as were multiple surgical procedures. High ICP may be a factor favouring the emergence of epilepsy (Faillace and Canady 1990). Bourgeois et al. (2004) followed 802 children treated with shunts for hydrocephalus of multiple causes for an average of 7.6 years (range 1–26 years). Seizures occurred in 255 of them (32%) and were recurrent and unprovoked in 27%. Seizures began before shunting in 29% and after shunting in 71%. All types of seizures were observed, with a predominance of focal seizures. The latter type was more frequent following shunting, while generalised seizures, often occasional, predominated before shunting. Hydrocephalus is one possible cause of continuous electrical status of slow sleep (Battaglia et al. 2005; see also Chapter 16). The incidence of seizures was higher in children who had shunt dysfunction and/or infection. A young age at operation and a higher incidence of shunt complications were associated with seizure frequency. In all cases the presence of epilepsy was a predictor of poor cognitive outcome.

Complications unrelated to shunt procedures

These are rarely observed now as virtually all cases of definitely progressive hydrocephalus are effectively treated with shunts or other methods. However, some complications can develop insidiously before treatment, including hemiplegia. There is an established relationship between hydrocephalus and the hemiplegic type of CP. In 28 cases of CP secondary to hydrocephalus investigated by O’Reilly and Walentynowicz (1981), 11 were of the hemiplegic type. In rare cases a puncture porencephaly can develop along the track of a ventricular needle or of a non-functioning catheter. In other children, hemiplegia may result from ependymal rupture with CSF dissection into the centrum semiovale or from the development of a diverticulum of the lateral ventricle, located in most cases at the level of the trigone on the internal aspect of the hemisphere, that may enter the posterior fossa (Naidich et al. 1982). Such diverticula may rupture into cisternal spaces and realise a spontaneous ventriculocisternotomy with stabilisation of the hydrocephalus. Occasional complications of unoperated hydrocephalus include IVH in the case of rapidly evolving hydrocephalus, and hydrosyringomyelia as a consequence of stabilised hydrocephalus (Olson and Milstein 1988). The latter may be associated with marked scoliosis that may improve with treatment of the hydrocephalus.

Overall outcome of hydrocephalus

Before the introduction of shunt treatment, fewer than 50% of live born term infants with hydrocephalus survived, whereas currently the mortality rate is between 10% and 15% (Fernell et al. 1986, 1994). At the same time, there has been a major decrease in the frequency of the characteristic major sequelae of chronic untreated hydrocephalus (Fernell et al. 1988). That study found frequencies of 8% and 18% respectively for ataxic and other forms of CP and of 21% and 16% respectively for mild and severe intellectual disability; epilepsy was present in 25% of survivors and visual difficulties with optic atrophy in 11%. Bourgeois et al. (1999) reviewed 802 children with operated hydrocephalus with a mean follow-up of 8 years. Thirty-two per cent developed epilepsy, usually severe. Epilepsy was more frequent in children with shunt complications. The presence of the shunt might be a factor, although this remains dubious. The incidence of the ‘cocktail party syndrome’ (children who talk a lot without listening while the content is superficial and without understanding) (Hagberg 1962) was only 3% as compared with 27% in the preshunting era. It seems likely that CP other than the ataxic form, intellectual disability, epilepsy and precocious puberty, none of which has decreased significantly since shunting was introduced, are attributable mainly to the brain pathology associated with hydrocephalus. In contrast, ataxia, strabismus and the cocktail party syndrome seem more directly related to unchecked long-standing intracranial hypertension and ventricular distension. Despite the improved outlook, recent work on unselected children with hydrocephalus showed that 47% had specific learning
Chapter 7 Hydrocephalus and Non-Traumatic Pericerebral Collections

...difficulties (Persson et al. 2007). Moreover, many patients with early-onset hydrocephalus tend to have fine motor dysfunction and/or uneven cognitive profiles with language better developed than nonverbal cognitive abilities (Op Heij et al. 1985), which are not necessarily reversed by shunting especially if it has been delayed or complicated. Some investigators have described a syndrome of nonverbal learning difficulties (Dalen et al. 2006).

Results of ventriculostomy appear to be satisfactory. A long-term outcome study of 975 consecutive children followed for a mean of 11 years included 280 treated with endoscopic third ventriculostomy and 695 treated with shunt insertions. (Beuriat et al. 2011). Those of shunting operations are still far from fully satisfactory. Kokkonen et al. (1994) had seven deaths among 42 children, and five of the survivors were institutionalised for severe cognitive impairment. Only one-third of these patients had vocational training, while a quarter stayed at home without meaningful activity. In the series of Mori et al. (1995), 22% of 1450 patients had intellectual disability. Poor results were correlated with age and cause of hydrocephalus, with the presence of epilepsy, with shunt complications and delay in their treatment, and with the degree of ventricular dilatation before shunt.

Even in children with effectively treated hydrocephalus who develop relatively normally, there is an overrepresentation of clumsiness and poor motor coordination. In most cases, the results on performance scales of IQ tests are lower than those on the verbal items (Billard et al. 1987; Fernell et al. 1988).

It is still uncertain whether treatment should aim at achieving a normal ventricular size; an important issue in view of the less marked decrease in ventricular size with ventriculostomy. Although children with moderate or severe ventricular dilatation do less well than those with normal-sized ventricles (Fernell et al. 1988), a number of associated factors can be responsible. Ventricular dilatation augments with operational delay and associated atrophy, which can also adversely affect the cognitive outcome, and there may be little correlation between ventricular size and intellectual function. At this stage, most surgeons believe that avoidance of the frequent and serious complications of shunts outweigh the undemonstrated effect of ventricular dilatation. Some patients who have a very large head and a thin cerebral mantle may be quite normal. Multivariate analysis of prognostic factors indicates that ventricular dilatation in itself explains from a statistical point of view only 20% of the ultimate variance of the results. Children with large ventricular size after shunting seem to do less well on nonverbal and visuospatial function tests, but the rest of their functions seem normal when aetiology and age at operation are taken into account (Billard et al. 1987).

The cause of hydrocephalus and the age of presentation are major prognostic factors. Fetal hydrocephalus has a particularly poor outcome (Mori et al. 1995). Preterm infants with ventricular haemorrhage currently represent a large group with a rather poor prognosis. Hislop et al. (1988) found that of 19 infants shunted for PHVD, 14 developed shunt complications and several had severe sequelae such as hypsarrhythmia and infantile spasms. Seventy-three per cent of the very preterm infants studied by Fernell et al. (1994) developed CP; 55% had intellectual disability, 52% epilepsy and 22% severe visual impairment. The prognosis is largely determined by the presence of other lesions associated with IVH such as periventricular leukomalacia (Ventriculomegaly Trial Group 1994). These are much more difficult to detect by ultrasonography than are haemorrhages so that the outcome may be difficult to predict.

Patients with postmeningitic or toxoplasmonic hydrocephalus also do rather poorly because of the usual occurrence in such cases of diffuse brain damage. It is difficult in many cases to assess the role of high pressure itself irrespective of the cause.

A significant number of the sequelae are no doubt due to repeated episodes of shunt dysfunction, which favours the use of endoscopic surgery. When a shunt is necessary, improvement of the material and methods of shunting is a high priority. Prevention of hydrocephalus can be achieved by measures such as earlier and better treatment of bacterial meningitis and prevention of haemorrhage. Prevention of preterm birth is a major target, as the majority and the most severe cases of hydrocephalus occur among small preterm infants.

**NON-TRAUMATIC PERICEREBRAL COLLECTIONS**

Pericerebral fluid collections represent one of the most common causes of large head size in infants and children. Since the widespread use of modern neuroimaging they have been recognised both in symptomatic and asymptomatic patients and can be divided into two broad groups: symptomatic cases that are associated with brain damage or genetic syndromes, and cryptogenetic cases that have been variously designated as benign subdural collections, benign external hydrocephalus (Alvarez et al. 1986), and benign extracerebral or extra-axial collections (Hamza et al. 1987). Most cases in the asymptomatic group can be considered as a variant of normal development and represent simple enlargement of the subarachnoid space. Reported frequencies for these groups vary. Symptomatic cases accounted for 13 of 94 patients (14%) in the series of Hamza et al. (1987) and for 36 of 63 patients (57%) in that of Alvarez et al. (1986).

The exact location of fluid is controversial (Aoki 1994). It is probably initially subarachnoid, but possible effraction into the subarachnoid space is sometimes demonstrated and may be spontaneous or due to additional minimal trauma as occurs also in cases of large subarachnoid cysts associated with subdural collections. The reasons for the anterior predominance and delayed effacement of the collections remain unclear.
Impairment of CSF resorption into the venous system as a result of increased venous pressure or increased resistance of the arachnoid villi has been speculated. The presence of fluid in the subdural space may be explained by a subarachnoid–subdural fistula with a one-way valve effect or by other, undefined mechanisms. Baraton et al. (1989) have shown that contrast injected into the lumbar space in 26 patients did not contaminate the peri-cerebral collections but remained limited to the anterior part of the pericerebral space underneath the pericerebral collection, therefore suggesting a subdural location.

The fluid is usually clear and the protein level normal or only slightly elevated. Ventricular dilatation of variable, but usually mild, degree may be associated.

PERICEREBRAL COLLECTIONS OF KNOWN CAUSE

These are usually associated with ICP and at times with some degree of internal hydrocephalus.

Abnormal Venous Return

This produces an increased volume of the intracranial venous blood compartment with consequent increase in intracranial contents and ICP. This in turn results in turgescence of the brain, which prevents or limits ventricular dilatation. Abnormal constriction and/or aberrant venous pathways rarely exist in isolation, but they may be associated with certain types of craniosynostosis (Sainte-Rose et al. 1984; Tanaka et al. 1985). Thrombosis of the superior vena cava, of jugular veins or of intracranial sinuses may also be a cause. Vena cava thrombosis is most often caused by indwelling central catheters used for drug infusion or parenteral feeding. Hydrocephalus from such causes is virtually always mixed internal and external. The external part, however, may communicate with the subdural space. Increase in pressure from large arteriovenous malformations, especially aneurysms of the vein of Galen, also produces external as well as internal hydrocephalus.

Achondroplasia

This disease is regularly associated with external hydrocephalus as well as ventricular dilatation (Pierre-Kahn et al. 1980). Increase in venous pressure is due to narrowing of the basal venous foramina. Such narrowing may also prevent dampening of CSF pulse pressure waves by immediate outflow of blood from the cranium. Treatment of external hydrocephalus of venous origin is based on reduction of venous pressure by cure of its cause or by bypass operation (Sainte-Rose et al. 1984).

Other Causes

These include venous hypertension due to thrombosis of the superior vena cava and various genetic syndromes such as the Sotos, Beckwith–Wiedemann, Goldenhar and Weaver syndromes (Alvarez et al. 1986) and organic acidurias, especially glutaric aciduria.

PERICEREBRAL COLLECTIONS OF UNKNOWN CAUSE

Cryptogenic or Benign Pericerebral Collections

Cryptogenic pericerebral collections are manifested clinically by a large head. Affected children often have head circumference above the 95th centile by 1 year of age, and tension of the fontanelle may be observed (Kumar 2006). Eventually, velocity of head growth decreases and the head growth curve becomes parallel to the normal growth pattern or tends toward normal. This phenomenon may be particularly striking in preterm infants. In 12 such patients followed by Al-Saedi et al. (1996), the head circumference stabilised between 15 and 18 months at the 95th centile.

Most infants have no abnormal neurological signs, but motor and sometimes language development may be delayed (Alvarez et al. 1986). The radiological signs include moderate enlargement of the pericerebral spaces, especially in the frontal or frontoparietal regions bilaterally and symmetrically, with interhemispheric sulcus dilatation extending posteriorly to the middle third of the brain.

There is often a mild dilatation of the ventricles. Differentiating benign enlargement of the subarachnoid space from subdural collections may be difficult. Colour Doppler ultrasonography show the veins crossing the pericerebral spaces in benign collections but not in subdural effusions (Aoki 1994; Chen et al. 1996). MRI shows a higher density of fluid and the presence of a dense external membrane (Wilms et al. 1993) in subdural fluid.

Although the causes of cryptogenic effusion are, by definition, unknown, a relationship to simple macrocephaly (Lorber and Priestley 1981; Gooskens et al. 1988) has been suggested. Alvarez et al. (1986) found a family history of large head in 32 of their 36 cases and suggested the existence of a continuum between collections and the familial megalencephaly. The occurrence of ‘external hydrocephalus’ in twins has been reported (Cundall et al. 1989).

The diagnosis of cryptogenic pericerebral effusion should exclude all known causes, particularly chronic traumatic subdural haematoma.

The course of pericerebral collections is regularly benign. The rare patients left with mild or, rarely, moderate intellectual disability (Hamza et al. 1987) may have been misclassified. Although surgical treatment has sometimes been performed (Tolias et al. 2000), spontaneous resorption is the rule and no treatment is justified.

REFERENCES


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Cerebral Palsy
and Related Movement Disorders

Ingeborg Krägeloh-Mann

Cerebral palsy (CP) is currently defined as a group of disorders of motor function, movement and posture; it is permanent but not unchanging; it is due to a nonprogressive lesion or abnormality in the developing/immature brain (SCPE 2000). The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, and by epileptic seizures as well as secondary musculoskeletal problems (Bax et al. 2005; Rosenbaum et al. 2007).

This definition is based on clinical phenomenology and clinical history. Additional features such as imaging or laboratory results are not primary inclusion criteria, but are important to further describe CP subgroups with respect to aetiology or at least pathogenesis. However, these investigative modalities are not available in all countries to the same extent and while their use has enhanced knowledge and understanding of CP pathogenesis, the findings and features do not form part of the CP definition. As CP epidemiology relies on standard inclusion and exclusion criteria, comparison between countries and time periods would be difficult if these features were part of the CP definition. Progressive conditions resulting in loss of acquired skills, spinal diseases and, in most countries, cases where hypotonia is the sole neurological finding are excluded. Neurological criteria define the subtypes (e.g. spastic, dyskinetic and ataxic; Hagberg and Hagberg 1993).

From a clinical viewpoint, the symptoms and signs of CP are not unchanging. The typical neurological signs take time to develop – (see Diagnosis and Differential Diagnosis of Cerebral Palsy section) – and it is generally agreed that the child should be at least 3 years of age before the CP diagnosis is established: CP registers accept children only at the age of 5 years (SCPE 2000; Stanley et al. 2000). Some slowly progressive conditions with early onset, such as hypomyelinating disorders, may still appear as a static condition clinically at the age of 5 years, which leaves a certain ‘grey zone’ when defining CP using clinical phenomenology only (Krägeloh-Mann et al. 1995).

The concept of CP is to some extent artificial, not only because the causes, mechanisms and consequences of the underlying brain pathology are multiple, but also because the age limit of brain immaturity is difficult to define. Usually there is a distinction between CP of postneonatal onset and CP due to pre-, peri and neonatal events, the latter being the basis for reported trends on CP prevalence, when not otherwise specified. Postneonatal CP should be distinctly addressed as causes are usually clearly defined. The age limit is somewhat arbitrary being dependent on what is understood as immaturity with regard to the brain. There are recommendations for using the term ‘postneonatal cerebral palsy’ such as onset being between 5 weeks postnatal and 2 years (SCPE 2000) or 2–3 years (Rosenbaum et al. 2007). Some countries do not include postneonatal CP but prefer to describe the clinical condition specifically, for example, hemiparesis due to stroke at a certain age.

PATHOLOGY, AETIOLOGY, PATHOGENESIS

Only elements that are operative in CP in general are discussed in this section. More detailed information is given in sections on the individual subtypes of CP.

Pathology is not specified in the definition of CP. Conventional neuropathology used to be the main informational source to describe pathological changes in CP. This has changed with the advent of neuroimaging, especially magnetic resonance imaging (MRI), which has a good potential to detect lesions or maldevelopments of the brain. Because the human brain undergoes complex organisational changes during intra- and extraterine development, the pathological patterns of abnormalities/lesions found will depend on the stage of brain development at the time of insult (Krägeloh-Mann 2004). The brain pathology of CP is to a large extent dependent on the time of occurrence of noxious events that interfered with the development of the brain or actually damaged it (see Chapters 1–3).
Pathology and Timing

Cortical neurogenesis takes place predominantly during the first and second trimesters, characterised by proliferation, migration and organisation of neuronal precursor cells, then neuronal cells. Disorders of this progress result in specific pathological patterns, that is, malformations of cortical development, such as lissencephaly, pachygyria or polymicrogyria. Some of these disorders may be of genetic origin, especially when symmetrical in extent (Kato and Dobyns 2003; Barkovich et al. 2012).

During the third trimester, when the ‘gross architecture’ of the brain (neural cyto- and histogenesis) is largely established, growth and differentiation events are predominant and persist into postnatal life (axon, dendrite and synapse formation, myelinisation). Disturbances of brain development during this period mainly result in clastic lesions. Their causes are multiple and key factors are inflammation with excessive cytokine production, oxidative stress and excess release of glutamate, triggering the excitotoxic cascade, factors that are induced by hypoxic–ischaemic and/or infectious mechanisms, whereby a potentiation of single effects can be assumed (Duggan et al. 2001; Johnston et al. 2001; Hagberg and Mallard 2005; Edwards and Tan 2006). Early in the third trimester, white matter is especially affected. The major neuropathology, that is often reported to result in CP includes periventricular leukomalacia (PVL) or complications of intraventricular haemorrhage (de Vries 1996; Olsén et al. 1998; Krägeloh-Mann et al. 1999; Stewart et al. 1999; Volpe 2009).

In the late third trimester the cortical grey matter, basal ganglia and thalamus appear to bear the brunt of damage (Keeney et al. 1991; Baenziger et al. 1993; Rutherford et al. 1995; Volpe 2001). Infarcts of the MCA are reported mainly in children born at or near to term with unilateral spastic CP (Hagberg et al. 1996; Govaert et al. 2000). They may also occur in the very preterm child, then involving more the lenticulostrate arteries (de Vries et al. 1997; Benders et al. 2009).

The different patterns of first, second and third trimester origin are indicated in Table 8.1 and Figure. 8.1.

Systematic reviews on MRI findings in children with CP (Krägeloh-Mann and Horber 2007; Korzeniewski et al.
2008; Reid et al. 2014) find a clear pathology indicating a specific pathogenesis in around 80% of cases, with a predominance of white matter lesions (around 50%), followed by predominantly grey matter lesions (around 20%) and maldevelopments of the brain (around 10%). Thus, the major pathology in CP is lesional, in the sense of clastic, affecting a primarily normal brain. The same lesional patterns tend to occur at the same gestational ages regardless of the time of birth. Thus, for example, PVL can occur in utero (in a term-born child) or peri- and neonatally.

Genetic origin, in contrast, plays a minor role. As indicated earlier maldevelopments of the brain resulting in CP may have a genetic or acquired background. For example, a child with bilateral spastic CP may have lissencephaly-pachygyria due to Miller Dieker syndrome, a 17p13.3 deletion syndrome (Spalice et al. 2009), or due to prenatal cytomegalovirus infection (Manara et al. 2011). The proportion of maldevelopments causing CP due to genetic changes is, however, not clearly known. In addition to monogenetic aetiologies of CP, there is a discussion that multiple genetic factors may cause the disorder, or may contribute to its underlying pathology (Moreno-De-Luca et al. 2012). A certain increased familial risk, after excluding preterm birth as an important risk factor for CP, has been reported not only for twins, but also for siblings and when the father or mother is affected (Tollanes et al. 2014).

The main findings in CP subtypes will be summarised here briefly (see also Table 8.2) with more detail given in the following paragraphs. Lesions (e.g. patterns of early or late third trimester origin), whether of pre- or peri-, neonatal timing, are found in bilateral spastic CP in more than 80%, in spastic hemiplegia in about 70–80%, in dyskinetic CP probably in more than 50%. Genetic and acquired CP of first or second trimester origin is found in around 10% of cases. Ataxic CP seems to form an exception within CP subtypes as morphological abnormalities are found in probably less than 50% of cases and are probably heterogeneous with some predominance of maldevelopments. This, together with a higher occurrence of familiarity suggests a mainly genetic origin. Taken together, CP, when phenomenologically defined, is mainly, but not exclusively, a lesional condition, and ataxic CP is clearly an exception.

### Table 8.1 Patterns of brain maldevelopment or lesions dependent on the stage of brain development

<table>
<thead>
<tr>
<th>Period</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st and 2nd trimester</td>
<td>Maldevelopment</td>
</tr>
<tr>
<td>Week 4–15</td>
<td>Anencephaly, heterotopias, schizencephaly</td>
</tr>
<tr>
<td></td>
<td>Lissencephaly, pachygyria, agenesis corpus callosum</td>
</tr>
<tr>
<td>Week 20–24</td>
<td>Polymicrogyria (until approx. week 28), hydrencephaly</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>White matter lesions predominant</td>
</tr>
<tr>
<td>Early 3rd trimester</td>
<td>Intracranial haemorrhage, periventricular infarction, periventricular leukomalacia</td>
</tr>
<tr>
<td>Week 24–30</td>
<td>Periventricular leukomalacia (in rare cases until week 38)</td>
</tr>
<tr>
<td></td>
<td>Thromb-embolic infarcts (rare)</td>
</tr>
<tr>
<td>Late 3rd trimester</td>
<td>Grey matter lesions predominant</td>
</tr>
<tr>
<td>Week 36–44</td>
<td>Cortico-subcortical lesions (parasagittal, multicystic encephalomalia, gyrus prae/postcentralis)</td>
</tr>
<tr>
<td></td>
<td>Basal ganglia/thalamus lesions</td>
</tr>
<tr>
<td></td>
<td>Thromb-embolic infarcts</td>
</tr>
</tbody>
</table>

The time periods indicated represent guidelines, but are not distinct, i.e. a certain overlap between time periods is biological.

### Table 8.2 ‘Lesional patterns’ in cerebral palsy-subgroups according to MRI

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Term</th>
<th>Lesion Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral spastic cerebral palsy</td>
<td>Term 15% 20%</td>
<td>1st/2nd trimester (e.g. focal cortical dysplasia)</td>
</tr>
<tr>
<td>Unilateral spastic cerebral palsy</td>
<td>Term 15–20%</td>
<td>1st/2nd trimester (e.g. focal cortical dysplasia)</td>
</tr>
<tr>
<td>Dyskinetic cerebral palsy</td>
<td>Term &lt;30% Preterm</td>
<td>Kernicterus has become rare</td>
</tr>
<tr>
<td>Ataxic cerebral palsy</td>
<td>Term Heterogeneous: CT/MRI in &gt;50% normal, in 30–40% cerebellar hypoplasia, probably mainly genetic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preterm Unclear</td>
<td>Unilateral spastic lesions, in single cases kernicterus, otherwise unclear</td>
</tr>
</tbody>
</table>

Updated from Krägeloh-Mann and Cans (2009).
MCA, middle cerebral artery; PVL, periventricular lesions; ICH, intracranial haemorrhage.
Prevalence of Cerebral Palsy

Incidence looks at the occurrence of new cases of a condition within a period of time, prevalence looks at those who currently have the condition during a particular period or at a particular date. In CP, it is typically prevalence that is measured and compared, the reference basis being mainly birth periods and place of residence at birth. This relates to the fact that the CP diagnosis is only possible with some delay between brain compromise and its obvious clinical signs, and some children may have died within this period (e.g. before CP diagnosis could be established). Data on prevalence of CP vary with the series studied and the period over which they are collected. Overall, CP prevalence is between 2 and 2.5 per 1000 live births, indicating that CP is the commonest cause of physical disability in early childhood (SCPE 2002; Stanley et al. 2000).

Studies of CP in relation to birthweight estimate that infants of very low birthweight (VLBW) (<1500g), are between 40 and 100 times more likely to have CP than normal birthweight infants (≥2500g). A combination of factors including decreased neonatal mortality and increased survival rates in VLBW infants, due to improved care of the preterm infant, lower accepted viability limits and an increase in multiple births, has resulted in a rise in the absolute number of VLBW infants at risk of CP.

Evidence from CP registers suggests that the prevalence of CP among VLBW infants rose over the 1980s (Pharoah et al. 1990; Hagberg et al. 1993; Stanley et al. 2000). This rise was probably due to the survival of very preterm infants of less than 1000g birthweight (Hagberg et al. 1989b). This was reported also for the 1990s (Doyle et al. 2000). Other studies, however, indicate that the rates of CP in VLBW infants are now decreasing (Krägeloh-Mann et al. 1994; Topp et al. 2001; Surman et al. 2003; Himmelmann et al. 2005).

As data from different registers and studies are difficult to compare, the Surveillance of Cerebral Palsy in Europe (SCPE) network was founded in 1998 to build up a common database among CP registers in Europe in order to describe trends in CP prevalence for different birthweight and gestational age groups on the basis of criteria cohorts with common inclusion and exclusion criteria. Results from the European database confirm this decrease: the decline in rate was seen in infants of 1000–1499g birthweight from 60 to 40 per 1000 live births from 1980 to 1996 or from 90 to 44 per 1000 neonatal survivors (NNS) (Platt et al. 2007) (Fig. 8.2).

Figure 8.2 Prevalence of cerebral palsy rates (3-year moving average) among infants of (a) <1000g birthweight and (b) 1000–1499g birthweight from nine European centres, 1980–96, showing the clear decline of prevalence in the first group. Reproduced from The Lancet, vol 369, Platt et al., Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study © 2007, with permission from Elsevier.
The trends in the rate of CP by gestational age mirrored that of birthweight. The moderately preterm group also showed a clear decrease from 10 to 6 per 1000 livebirths from 1980 to 1998 (Andersen et al. 2011). Interestingly, CP rates in the 1990s in this European cohort did not differ much in children of birthweight less than 1000g from those in children with birthweight 1000–1500g. Recent data from the SCPE, analysing birth years until 2003, indicate that this decline continued for children of LBW and VLBW and resulted for the first time in a significant decrease of total CP prevalence from 1.90 to 1.77 per 1000 livebirths (1980 to 2003) (Sellier et al. 2016). A recent report of the Australian CP network based on children born 1993–2006 showed trends per birthweight very similar to the European study (ACPR 2013).

This indicates that while the survival of infants of low birthweight or gestational age continues to improve, this continued improvement is not at the expense of increased morbidity, but results since the late 1990s in a decrease of neurological morbidity. Also for the first time, this also resulted in a decrease of overall CP prevalence. So, the usual conclusion in reviews on CP, that its prevalence remains constant (Oskoui et al. 2013), can now be updated. Cerebral palsy prevalence data from population-based studies, thus, provide a more global view of the impact of the neonatal intensive care on survival and quality of survival in the last two decades.

### CLASSIFICATION OF CEREBRAL PALSY

Attempts at classification of CP have been multiple (Ingram 1966) and no system is fully satisfactory. Even with the broader availability of neuroimaging, especially MRI, an aetiological classification is not useful, first because of a different availability of MRI in different countries and second because of the fact that universally accepted standards such as a neuroimaging classification for CP are not yet available.

In addition, similar aetiological factors, for example PVL, can lead to a different clinical picture dependent on the lesion extent and topography. And different aetiological factors, for example a stroke in the domain of the MCA or focal cortical dysplasia in the motor area can lead to a similar clinical picture, spastic hemiplegia, or unilateral spastic cerebral palsy (US-CP).

A clinical, phenomenological classification, therefore, is more useful than aetiological or pathological ones. It makes comparison between different countries with different standards of medical care more feasible and, what is more important, allows grouping of children with similar neurological involvement necessitating similar therapeutic interventions and leading to similar outcome. In the clinical routine, it is recommended, however, to add, if possible, aetiology or pathology to the clinical CP diagnosis; for example, spastic hemiplegia/US-CP due to an infarct of the MCA (see Diagnosis and Differential Diagnosis of Cerebral Palsy section).

Cerebral palsy is usually classified into neurologically defined subtypes, for example, spastic, dyskinetic and ataxic (Hagberg and Hagberg 1993). There is a variety of subdivisions within spastic CP:

- hemiplegia, hemiparesis, describing unilateral involvement with the addition of ‘arm’- or ‘leg-dominated’ to describe topographical involvement;
- diplegia, diparesis or tetraplegia and quadriplegia, describing bilateral involvement; the first two meaning that legs are more involved than arms, the latter that arms are as much or more involved than legs.

Usually, mild, moderate or severe grades which are added to describe functional severity. However, these terms are not easily applied in a standardised way and attribution to the clinical situation is subjective. Thus, for example, rates of diplegia versus tetraplegia between different centres may vary from 20 versus 80, to 80 versus 20 (Colver and Sethu-madhavan 2003).

Therefore SCPE recommended to use the terms uni- or bilateral spastic CP and describe functional severity in legs and arms according to standardised scores (SCPE 2002) such as the Gross Motor Function Classification System (GMFCS; Palisano et al. 1997) and the Bimanual Fine Motor Function System (BFMF; Beckung and Hagberg 1992) or the Manual Ability Classification System (MACS; Eliasson et al. 2005). The combination of functional scores for arms and legs could give a clinical picture for the clinician, for example, higher scores in the legs describe diplegia or leg-dominated bilateral cerebral palsy (BS-CP) (Krägeloh-Mann et al. 1993), the prerequisite would be that scores are equivalent for legs and arms which is, however, not unchallenged.

When the neurological features are not purely attributable to one of the neurological categories, the predominant type should determine the classification. This can be especially difficult, when spasticity and dystonia occur together, so that a spastic-dystonic subgroup has been recognised (Hagberg and Hagberg 1993; Krägeloh-Mann et al. 1993). In such a situation, dystonia usually affects face and arms, whereas spasticity is predominant in the legs, with some involvement of the arms also. Thus, with respect to predominance, these children can be usually classified as having predominantly spastic CP.

The clinical picture of CP is often not only characterised by motor function problems but also by additional disturbances of sensation, cognition, communication, perception and/or behaviour and/or by a seizure disorder, which determine prognosis and treatment and have to be taken into account in the individual assessment of the patient and the multidisciplinary therapeutic approach (SCPE 2002; Rosenbaum et al. 2007).

In the clinical context, classification – and diagnosis – of a child with CP is recommended to respect to following domains:

1. Neurological subtype, spastic unilateral or bilateral, dyskinetic or ataxic;
2. Severity of motor dysfunction according to GMFCS BFMF, or MACS;
3. Additional impairments of vision, cognition, seizure disorder;
4. Child being born term or preterm and indication of possible complications; and
5. Aetiology or pathology according to imaging results.

THE VARIOUS TYPES OF CEREBRAL PALSY

In the following section the subtypes of CP are described with respect to their prevalence, their motor dysfunction and the presence of additional impairments and with respect to neuroimaging findings. Spastic forms account for the majority (a little less than 90%) of cases, around one-third being unilateral and around two-thirds bilateral; dystonic forms occur in around 7% and ataxic in around 4% (Hagberg and Hagberg 1993; SCPE 2000, 2002; Sellier et al. 2016). As it is difficult to verbally describe movements disorders, the European network SCPE within the process of consensus building and harmonising CP definition and classification has established a reference and training annual which illustrates the neurological subtypes of CP with video examples and also gives typical case descriptions; this manual is accessible for health professionals: www.scpenetwork.eu.

SPASTIC CEREBRAL PALSY

The neurological symptoms in spastic CP are as follows (Platt et al. 2009; SCPE 2000):

• increased tone characterised by increased resistance to passive movement which is velocity dependent (Sanger et al. 2003);
• pathological reflexes; for example, increased reflexes or hyperreflexia and pyramidal signs, for example, Babinski response;
• abnormal pattern of movement and posture, in lower limbs characterised by equinus foot, crouch gait, internal rotation and hip adduction, in upper limbs by arms in flexion, hands fisted with thumb adducted or stiff and poorly directed movements of fingers.

BILATERAL SPASTIC CEREBRAL PALSY

BS-CP is especially prevalent in preterm born children. The overall prevalence is 1.2 per 1000 livebirths – around 0.3 per 1000 livebirths in children with normal birthweight, 6–10 per 1000 livebirths in children with moderately reduced birthweight and around 40–60 per 1000 livebirths in very low birthweight children (Platt et al. 2007; Andersen et al. 2011). Interestingly, the decrease in prevalence reported above in preterm born children with CP was especially due to a decrease in BS-CP.

Clinical Findings

As studies on clinical findings used different nomenclature, the terms diplegia, diparesis and leg-dominated are summarised in the following as milder forms and tetra- or quadriplegia as severe forms and data are specified when functional scores were applied. The milder forms, (GMFCS scores I–III), are most common. In most studies they account for around 60% of BS-CP cases and are typical for the preterm born child (Fig. 8.3). The severe forms often have some additional impairment and occur more often in the term-born child (Krägeloh-Mann et al. 1993; Horber et al. 2016). In the severe forms, additional dystonic features, which affect hands, face and even trunk, are common so that the delineation towards dystonic CP is not always clear cut.

Motor deficit is severe in more than two-thirds of children in the sense that they cannot walk without aid at the age of 5 years (Krägeloh-Mann et al. 1993). Contractures develop frequently, especially in children who do not learn to walk, in equinus position, hip adduction knee flexion, and so forth.

Additional impairments occur clearly more often, when gross motor dysfunction is more severe, which indicates that the more severe the brain lesion, the more severe are not only the motor, but also additional deficits (Surman et al. 2009; Horber et al. 2016). Cognitive problems in the sense of learning difficulties (corresponding to an IQ between 85 and 70) or intellectual disability (corresponding to an IQ<70) are encountered especially in the children with severe forms (e.g. 20% and 70%), whereas 40% of children with leg-dominated BS-CP have normal intelligence, 20% have learning difficulties and 40% intellectual disability (Krägeloh-Mann et al. 1993). Severe cerebral visual problems are encountered.
especially in the children with severe forms, around half of these children are blind or nearly blind; this is found in less than 10% in children with milder forms. Hearing problems (deaf or near deaf) are, however, not frequent, occurring in around 3% (Krägeloh-Mann et al. 1993). Epilepsy is encountered in around one-third of children with BS-CP and West syndrome in about 10%. Epilepsy is probably mainly symptomatic, as it is related to the severity of functional disability and to the extent and topography of causative lesions – children with BS-CP and epilepsy have a severe motor disability in 85% and a learning difficulty or intellectual disability in 90%; 100% of children with West syndrome have intellectual disability (Krägeloh-Mann et al. 1993).

Aetiology and Pathogenesis of Bilateral Spastic Cerebral Palsy

BS-CP is especially frequent in preterm born children, around 60–70% of children with CP in the different low birthweight groups have BS-CP (Sellier et al. 2016), often referred to as diplegia (Ingram 1964; Bennett et al. 1981). Systematic reviews of MRI in CP and population-based studies (Krägeloh-Mann et al. 1995; Krägeloh-Mann and Horber 2007; Korzeniewski et al. 2008; Himmelmann and Uvebrant 2011; Reid et al. 2014) show that genetic, first and second trimester abnormalities are rare, whereas white matter lesions are predominant and account for around 90% of findings, mainly the MRI PVL (Figs 8.4 and 8.5). As discussed in the Pathology, Aetiology, Pathogenesis section, the origin of white matter lesions are multiple and key factors are inflammatory. There is evidence that PVL is frequently accompanied by neuronal/axonal disease, affecting not only the cerebral white matter, but also thalamus, basal ganglia, cerebral cortex, brainstem and cerebellum. This constellation of PVL and neuronal/axonal disease has been termed ‘encephalopathy of prematurity’ and is supposed to be a complex amalgam of primary destructive disease and secondary maturational and trophic disturbances (Volpe 2009). The timing of this lesion is also a topic of controversy. A prenatal origin has been reported (Sinha et al. 1990; Iida et al. 1993). From hospital-based studies, however, there is evidence for a decrease in PVL (Hamrick et al. 2004). Also, van Haastert et al. (2011) described a decrease in cystic PVL of more than 50% between birth periods 1990–1993 and 2002–2005, whereby the severe form, cystic PVL III, showed the most significant decrease (ten-fold). The decreasing prevalence of BS-CP in the low birthweight children on a population basis is in accordance with the hospital-based observation that PVL is decreasing. PVL is typically bilateral, thus, when it affects the motor tracts, it usually gives rise to BS-CP (Fig. 8.5). These data of decreasing PVL and BS-CP argue against a primarily prenatal origin.

In term-born children with BS-CP, the systematic reviews of magnetic resonance findings show somewhat more heterogeneous results (see Table 8.2): maldevelopments of the brain with a genetic origin or originating in the first and second trimester account for around 15% of cases, examples are schizencephaly, lissencephaly and polymicrogyria. About 40% show predominantly white matter lesions, thus, patterns of early third trimester origin, most often magnetic resonance correlates of PVL a prenatal origin, thus, can be assumed. Around a third of the term-born children with BS-CP show lesional patterns characteristic of the more mature child indicating late third trimester or peri- and neonatal compromise (parasagittal

![Figure 8.4 Periventricular leukomalacia of three severity patterns (all axial T2-weighted images). (a) Mild very asymmetrical periventricular leukomalacia affecting the motor tracts only on one side (thick arrow), thus giving rise to unilateral spastic cerebral palsy, the frontal gliosis (thin arrow) supports the periventricular leukomalacia diagnosis; (b) mild symmetrical periventricular leukomalacia with bilateral gliosis but no white matter reduction giving rise to bilateral spastic cerebral palsy; (c) severe periventricular leukomalacia with irregular enlargement of lateral ventricles due to white matter reduction and periventricular gliosis giving rise to severe bilateral spastic cerebral palsy.](image-url)
injury, multicystic encephalomalacia, basal ganglia and thalamus lesions with involvement of the central sulcus) (Figs 8.6 and 8.7). Often a history of hypoxic–ischaemic encephalopathy or shock confirms the peri- or neonatal origin.

**CORRELATION BETWEEN MORPHOLOGY AND FUNCTION AND PREDICTION OF OUTCOME**

Severe motor disability (defined as inability to walk at the age of 5 years) is found in about 80–100% of children who have brain maldevelopments or predominantly grey matter lesions but also in about 70% of cases in severe PVL (PVL with global extensive reduction of white matter as indicated in Figs. 8.4 and 8.5) (Krägeloh-Mann et al. 1995; Reid et al. 2014). Children with mild PVL (periventricular gliosis without white matter reduction as indicated in Figs. 8.4 and 8.5) or PVL with only focal extensive reduction of white matter (moderate PVL) have severe motor disability in only one-third of cases. The degree of motor deficit in children with PVL is clearly related to the lesion extent within the pyramidal tracts (Staudt et al. 2000). Studies using diffusion tensor imaging have shown that PVL, which is usually more extensive when it reaches the parieto-occipital area, also involves thalamocortical pathways, which seems to be related to sensory changes (Hoon et al. 2009).

Cognitive impairment is again especially found in the children with brain maldevelopments and children with predominantly grey matter lesions (in up to 100%), but also in 90% of children with severe PVL; whereas normal cognitive outcome...
Severe visual impairment (visual acuity ≤0.3) is associated either with bilateral involvement of the optic cortex or with severe involvement of the optic radiation, which means bilateral widespread occipital cortical damage or extensive occipital white matter reduction in severe PVL. Mild PVL is usually not associated with visual impairment, especially not to severe visual impairment, but there is evidence for secondary visual problems, for example, in the domain of visual perception (for a review see Pavlova and Krägeloh-Mann 2013).

Neonatal imaging is important for the prediction of BS-CP and its severity. It has a good potential to identify lesions, especially when they are severe and after the first evolution of these lesions. For example, Figure 8.8 illustrates severe, cystic PVL and parasagittal injury as seen late in the neonatal period. Figure 8.9 shows the development of a basal ganglia and thalamus lesion involving also the central sulcus and is discussed in detail below in the section on dyskinetic CP.

See also neonatal imaging findings in the Diagnosis and Differential Diagnosis of Cerebral Palsy section.

## Unilateral Spastic Cerebral Palsy or Hemiplegia

The prevalence of US-CP, or hemiplegia, hemiparesis, is reported in the European survey to be about 0.6 per 1000 live births (SCPE 2000). It typically occurs in the term-born child. About one-third of cases are preterm born (Horber et al. 2016) and in contrast to BS-CP, the prevalence of US-CP in preterm cases, is not decreasing (Platt et al. 2007; Andersen et al. 2011).

**Clinical Findings of US-CP**

Clinical descriptions of US-CP often specify whether it is arm- or leg-dominated, whereby arm-dominated forms have been more often reported in term-born and leg-dominated
Neurological Consequences of Prenatal, Perinatal and Early Postnatal Interference with Brain Development

**Figure 8.9** Upper panel: Early images of bilateral basal ganglia and thalamus lesions in a term-born child after asphyxia and hypoxic–ischemic encephalopathy. MRI on day 4 abnormalities are seen on diffusion weighted images (here, ADC-maps) in basal ganglia and mediodateralthalamus (white arrows) and also in the central region (right, arrow), whereas T1-weighted (T1w) image (middle) does not show clear signal change. Lower panel: MRI on day 18 in the same child reveals the abnormalities clearly on T1w (middle and right), but no longer in diffusion weighted images (left).

Forms in preterm born children (Uvebrant 1988; Bouza et al. 1994a) (Fig. 8.10). Facial palsy is not seen in US-CP in contrast to acquired forms of postneonatal origin where it is often seen (Brown et al. 1987).

Motor deficit is rarely severe; fewer than 2% of children in the population-based series of Uvebrant (1988) did not walk at the age of 5 years; more than half could walk without much restriction, 30% had a moderate limp and 10% a severe limp. In around a half, hand function was described as quite good with single finger movements possible; only 20% did not have more than holding function. Sensory problems were reported in around 20%, they add to the functional deficit and should be carefully sought, for example, by discrimination tests such as 2-point discrimination, younger children can be asked to recognise objects when given in the normal or the paretic hand. Secondary motor problems with contractions are mainly seen in the paretic foot with equinus position; hip subluxation is not a frequent problem. Hypotrophy of the affected limbs is often seen, but correction of leg length is seldom necessary.

Cognitive problems in the sense of learning difficulties or intellectual disability are less often found in children with US-CP than in other CP forms. Uvebrant (1988) found mild intellectual disability in 12% of his preterm children with US-CP; 6% of the term-born children had

**Figure 8.10** Unilateral spastic cerebral palsy. A 7-year-old boy with left unilateral spastic cerebral palsy pre-dominating markedly in upper limb (right). Typical attitude of hand in patient with right hemiplegia (above). (Courtesy of Dr J-P Padovani, Hôpital des Enfants Malades, Paris.)
severe intellectual disability and 13% had a mild intellectual disability. In the SCPE database (until birth years 2003), around 70% had normal cognitive development, around 20% had a learning difficulty or mild intellectual disability and less than 10% had more severe cognitive problems (Horber et al. 2016). This means that around 85–90% of children with US-CP do not have intellectual disability and more than two-thirds have a normal cognitive development.

Severe cerebral visual problems are rare, reported mainly in term-born children, at a prevalence of around 5%. Hemi-anopsia is probably often overlooked as it is well compensated for by the children and only recognised when specifically looked for. The neuroimaging may give a hint when the optic radiation or visual cortex is clearly affected on one side due to, for example, a porencephalic lesion or an extensive infarct.

Epilepsy is a major comorbidity in US-CP, it is found in around a third of the children; 25% of them have severe epilepsy (Uvebrant 1988). Epilepsy is mainly symptomatic and more often encountered in US-CP due to cortical malformations or due to cortical lesions.

**Aetiology and Pathogenesis of US-CP**

MRI studies in children with US-CP (Krägeloh-Mann and Horber 2007; Reid et al. 2014) show abnormal results in a high percentage (around 90%) (Table 8.2). Brain maldevelopments account for around 15–20% of cases, mainly cortical dysplasias, but also unilateral schizencephaly and other forms of focal cortical dysgenesis. White matter lesions are seen in more than one-third, such as focal periventricular gliosis or focal periventricular tissue loss with or without gliosis. The latter typically are sequelae of intraventricular haemorrhages grades III and IV (haemorrhagic infarction) (de Vries et al. 1999). To a minor degree, very asymmetrical PVL may be responsible affecting the motor tract only in one hemisphere (Figs 8.4 and 8.5). Another third have infarcts of the MCA (Fig. 8.11). Again, as in BS-CP, there is a clear difference between preterm and term US-CP. White matter lesions occur significantly more often in preterm US-CP than in term (around 90% versus 20%). Whereas infarcts are reported less often in preterm children with US-CP in population-based studies. From a neonatologist point of view, however, where children are recognised with infarcts, when they are symptomatic in the neonatal period, up to 40% are reported with a gestational age below 37 weeks. Benders et al. (2009) reported infarcts of the main branch of the MCA to be characteristic for the moderately preterm child (>33 weeks) and involvement of the lenticulostriate branches for the more immature child. Taken together, also in US-CP, patterns of third trimester origin (e.g. clearly acquired patterns), are predominant and found in about two-thirds of patients.

In contrast to the observed decrease of PVL, there is no clear evidence for a decrease of severe IVH in the preterm infant during the same time period (Fanaroff et al. 2007; Rieger et al. 2012), which is likely to explain that prevalence of preterm US-CP is not decreasing.

**Correlation Between Morphology and Function and Prediction of Outcome**

A good correlation between extent of lesion and deficits has been found. In periventricular lesions, motor deficit for the arm and leg respectively was described as clearly related to the extent of the lesion within the pyramidal tract (Staudt et al. 2000). Cognitive impairment (learning disability or intellectual disability corresponding to an IQ<70) is most frequent in brain maldevelopments (60%), it occurs in about 40% in children with an infarction of the MCA and also in the group with considerable ventricular enlargement (it is noteworthy, that this ventricular enlargement is not purely unilateral in most of the children). In children with focal periventricular gliosis, normal cognitive functioning is found in more than 80%.

When periventricular haemorrhagic infarction is seen in neonatal imaging, asymmetrical myelination of the posterior limb of the internal capsule is an early predictor of US-CP (de Vries et al. 2005).

**Unilateral Spastic Cerebral Palsy: a Model to Study Neuroplasticity Motor Function**

The compensatory potential of the young nervous system following brain injury is considered to be superior to that of the adult brain (Kennard principle; Kennard 1936). The malformations and lesions, which characterise pathogenic events at different times during early brain development, offer a good model to study compensatory mechanisms of the developing brain. The healthy hemisphere plays an important role in the development of the other hemisphere.
role after unilateral lesions within the central motor system. In smaller lesions, not disrupting the motor tracts, an enlarged motor network involves also the healthy hemisphere (Staudt et al. 2002a). However, this is also described in adult patients following stroke (Weißler et al. 1993). In larger lesions, disrupting the motor tracts, abnormal fast conducting corticospinal projections from the healthy hemisphere exert the primary motor control. Such ipsilateral projections are physiological in the neonate; they do not mature and can no longer be elicited in later normal development (Eyre et al. 2001). They can apparently be maintained under pathological conditions, (e.g. when the contralateral projections are severed) (Farmer et al. 1991; Carr et al. 1993). However, their functional role seems to decrease already during late gestation, as Staudt et al. (2004) found evidence that hand function in patients with ipsilateral projections correlated with the timing period of the underlying brain lesions. In contrast to the motor system, there is no evidence that function can be reorganised interhemispherically (Wilke et al. 2009; Juenger et al. 2012).

Language in Unilateral Spastic Cerebral Palsy

In US-CP due to lesions acquired until the neonatal period, there is no gross difference in language with the hemisphere affected (Rankin et al. 1981; Aram et al. 1985; Carlsson et al. 1994) and there is good evidence that language in such a situation can be reorganised to the right hemisphere (Staudt et al. 2002b; Liegeois et al. 2004; Lidzba and Krägeloh-Mann 2005; Lidzba et al. 2013). However, this may be at the expense of originally right hemispheric functions, as visuospatial functions can be shown to be mildly deficient and there is evidence that this is correlated to the degree of right hemispheric language reorganisation and not to the overall lesion size (Lidzba et al. 2006). This supports the concept of ‘crowding’ initially proposed by Teuber (Teuber 1974; Lidzba and Krägeloh-Mann 2005). Children with left hemispheric lesions are reported to be slower in language development (Chilosi et al. 2001), which may indicate that the right hemisphere is not equally able to process language as the left hemisphere. And the evidence that complex linguistic processing is not as good when language is organised in the right hemisphere supports the concept that the left hemisphere has a genetic predisposition for language processing (Schwilling et al. 2012; Lidzba et al. 2013). Although there is no gross difference in language with the hemisphere affected, impairment of both verbal and nonverbal IQ is greater in children with left hemisphere lesions, while visuospatial functions are equally affected with lesions of either side (Vargha-Khadem et al. 1985; Carlsson et al. 1994). Speech and language defects are, of course, also related to the severity of intellectual disability. Taken together, language reorganisation to the healthy right hemisphere is a unique example of superior plasticity of the young brain, although there is evidence that the right hemisphere is not equally competent for language processing. The question still to be answered is up to what age can language be taken over by the right hemisphere without overt dysfunction occurring?

DYSKINETIC CEREBRAL PALSY

Prevalence of dyskinetic CP was reported to be 0.1 per 1000 livebirths in the European series (SCPE 2002; Himmelmann et al. 2009). It is reported especially in term-born children, who account for around 70% of children with dyskinetic CP. A significant increase in prevalence, from 0.05 to 0.12 per 1000 livebirths, occurred between 1976 and 1996 in children with a birthweight ≥2500g, whereas in the children with BS-CP and normal birthweight prevalence did not change during this period, which was also characterised by a significant decrease of mortality in the normal birthweight group.

Clinical Findings in Dyskinetic Cerebral Palsy

Dyskinetic CP (Fig. 8.12) is characterised by involuntary, uncontrolled, recurring, occasionally stereotyped movements, primitive reflex patterns predominate, muscle tone is varying (SCPE 2000). The European CP network recommends to sub-classify, if possible, into dystonic and choreoathetotic CP.

Dystonic CP is dominated by abnormal posturing and may give the impression of hypokinesia; fluctuating tone is characterised by easily elicitable tone increase; involuntary movements or distorted voluntary movements are typical and abnormal postures are due to sustained muscle contractions leading to slow rotation, extension or flexion of body parts.

Choreoathetotic CP is dominated by hyperkineties and tone is fluctuating but mainly decreased; ‘chorea’ means rapid
involuntary, jerky, often fragmented movements, ‘athetosis’ means slow, constantly changing, writhing or contorting movements.

Pure dyskinetic movement disorders do not show hyperreflexia with clonus or pyramidal signs. But in dyskinetic CP, these spastic signs may be present indicating some involvement also of the pyramidal system. As reported above, severe BS-CP is very often characterised by additional dyskinetic more specifically dystonic features. So allocation to spastic or dyskinetic CP may be difficult. It is recommended that subtype classification be determined according to the dominating features. Dystonic CP is very similar to severe BS-CP with respect to its functional problems and severity, as described above. Children with choreoathetotic CP may be less severely affected and may learn to walk without aids. Children with dyskinetic CP in general are characterised by global movement disorders that also involve facial expression and because they have great problems in expressing themselves, they are often misjudged with respect to their cognitive capabilities. Kernicterus, now a rare aetiology of CP (see Aetiology and Pathogenesis section) is typically characterised also by hearing loss.

Aetiology and Pathogenesis of Dyskinetic Cerebral Palsy

Epidemiological studies show that perinatal adverse events in dyskinetic CP of normal birthweight are more frequent than in BS-CP of normal birthweight; for example, convulsions before day 3 occurred in 76% versus 25% and an Apgar less than 5 at 5 minutes in 43% versus 9% (data from the European series in the birth years 1991–1996; Himmelmann et al. 2009). Together with the data on increasing prevalence of dyskinetic CP paralleled by decreasing mortality in normal birthweight children (see Prevalence section), it can be assumed that a higher survival of perinatal adverse events has lead to a higher morbidity.

In accordance with these epidemiological data, systematic studies of imaging findings in dyskinetic CP (Yokochi et al. 1991; Himmelmann et al. 2007) show in term-born children mainly lesions which are typical sequelae of severe asphyxia or shock with consequent hypoxic–ischaemic encephalopathy (lesions of late third trimester origin): bilateral involvement of the medio lateral thalamus and posterior putamen and pallidum (Fig. 8.7, Table 8.2), often associated with cortical–subcortical lesions, around the sulcus centralis; the diencephalic lesions may be subtle and thus missed when not looked for or when imaging quality is not very good. Because of monitoring and treatment of hyperbilirubinemia in the neonatal period, a typical pathology leading to dyskinetic CP, kernicterus, has become very rare. MRI typically shows hyperintensity of the globus pallidus on both sides (Govaert et al. 2000) and is, thus, distinct from the typical hypoxic–ischaemic pattern involving the putamen and the thalamus.

Preterm born children with dyskinetic CP are rarely reported and imaging findings in these children are even less systematically discussed. Kernicterus is also reported in preterm born children (Govaert et al. 2000); and basal ganglia and thalamus lesions can occur in the more mature preterm child (Bax et al. 2006).

Morphology–Function Relationship and Prediction of Outcome

Functional deficit can be relatively well predicted in these basal ganglia and thalamus lesions (Krägeloh-Mann et al. 2002). Children with a pure involvement of the diencephalic structures with subtle putaminal and thalamic lesions may learn to walk independently, although they always develop a general, mainly choreoathetotic movement disorder and have a high chance for normal or only mildly impaired cognitive functioning. This observation seems very important as cognitive development is often misjudged in these children who cannot express themselves because of their general dyskinetic movement disorder, which may impact on speech considerably. When diencephalic lesions get more extensive, usually also accompanied by cortico–subcortical lesions in the central region, children develop more severe motor problems (e.g. no independent walking (GMFCS levels III and IV), often not even trunk control (GMFCS V)) and also cognitive problems (e.g. severe intellectual disability), bulbar signs are then frequent leading to swallowing and severe speech problems. But even in these situations it is recommended to evaluate carefully what the child can understand, as it is often underestimated. Neonatal MRI in this lesion type is helpful for the prediction of outcome. Lesions here are best seen on T1 weighted images (~4–7 days after the acute event; Rutherford et al. 2005) (Fig. 8.9). This is important to know, as in contrast later images, for example, after the first year of life, show lesion best on T2-weighted images (Fig. 8.7). Very early imaging during the first week after the acute event, usually the first week of life, needs diffusion-weighted images to reveal the lesion (Rutherford et al. 2005). A myelin signal in the posterior limb of the inner capsule predicts the ability to walk at the age of 2 years, whereas severe diencephalic lesions together with cortico–subcortical lesions predict CP with severe motor impairment with high accuracy (Martinez-Biarge et al. 2012).

ATAXIC CEREBRAL PALSY

Ataxic CP, called by some authors nonprogressive congenital ataxia (Esscher et al. 1996; Steinlin et al. 1998), occurred in 0.09 per 1000 live births in the European series (SCPE 2002), which means that 4.3% of all individuals with CP had this specific subtype.

Clinical Findings of Ataxic Cerebral Palsy

Ataxic CP is characterised by loss of orderly muscular coordination, so that movements are performed with abnormal amplitude, rhythm and accuracy (SCPE 2002). Typical features include trunk ataxia that leads to disturbed balance. In the upper limbs a characteristic feature is past
pointing, that is, over- or undershooting of goal-directed movements; tremor is another common sign, mainly a slow intention tremor. Low tone is also a prominent feature. Motor development is usually clearly impaired and 10–25% are reported not to learn to walk independently (Steinlin et al. 1998; Horber et al. 2016). In the above mentioned studies, cognitive function was in the range of intellectual disability in two-thirds of cases, which was severe in half of these; visual problems were described in over 50% and 20–30% developed epilepsy. The clinical features vary from case to case. Most cases of nonprogressive cerebellar ataxia are congenital even though the clinical manifestations often do not become suggestive before 1 or 2 years of age, at the time when children normally begin to walk.

Aetiology and Pathogenesis of Ataxic Cerebral Palsy

Nonprogressive ataxia is an obviously heterogeneous condition (Table 8.2). Its pathogenetic mechanisms are poorly known and its nosological interpretation is controversial. The results described here, rely mainly on two studies (Steinlin et al. 1993, 1998; Esscher et al. 1996), which describe imaging findings in children with nonprogressive cerebellar ataxia. In contrast to the other CP types, a lesonal pattern in ataxic CP is exceptional. In more than 50% of cases, Computed tomography (CT) or MRI may show a normal result; in about 30–40% cerebellar hypoplasia of variable degree is found, which is not related to the degree of the motor involvement. Cerebellar lesions are increasingly recognised in the very preterm born child (Limperopoulos et al. 2007). Cerebral palsy in these children is often spastic (BS-CP) due to additional supratentorial white matter lesions (Krägeloh-Mann et al. 1999; Messerschmidt et al. 2008). When the latter do not affect to motor tracts, or when there are exclusively cerebellar lesions, the children are characterised rather by intellectual disability than by ataxia (Krägeloh-Mann et al. 1999; Limperopoulos et al. 2007). Thus, ataxic CP due to cerebellar lesions seems not a frequent finding in the very preterm born child. The familiarity in both term and preterm cases is high, thus, a probably mainly genetic origin of ataxic CP has to be assumed.

Prenatal factors play a dominant role in the aetiology of nonprogressive cerebellar ataxia (Hagberg et al. 1975b; Sanner 1979; Clement et al. 1984; Kvistad et al. 1985; Wichman et al. 1985; Tomiwa et al. 1987) which is supported by the predominant imaging findings discussed above. Obvious prenatal factors were present in 25% of the cases of Hagberg et al. (1975b) and, in 41% of patients, no cause was obvious but a prenatal origin was probable. Genetic factors were found in many series (Hagberg et al. 1972; Sanner 1973; Sanner and Hagberg 1974; Clement et al. 1984; Kvistad et al. 1985; Wichman et al. 1985; Tomiwa et al. 1987). Familial congenital nonprogressive ataxia has been reported from many parts of the world and autosomal recessive (Mathews et al. 1989; Pascual-Castroviejo et al. 1994), autosomal dominant (Furman et al. 1985; Tomiwa et al. 1987) and X-linked dominant (Fenichel and Phillips 1989) or recessive (Young et al. 1987) cases are on record. The correspondence between pathology (atrophic or dysplastic) and mode of inheritance is poorly documented (Guzzetta et al. 1993). Sporadic cases are common.

On the basis of these findings, which illustrate that ataxic CP stands out from the other CP subtypes insofar as it is rarely lesonal, probably often genetic and imaging findings do not predict functional deficits, the question arises, whether ataxic CP should rather be excluded from CP and described as nonprogressive cerebellar ataxia. Inclusion of ataxic CP within the CP concept relies on the fact, that the latter is still based on phenomenological criteria which constitute a useful sociomedical framework for certain children with motor disability with special needs, as stated at the beginning. And a classification based on aetiology or pathogenesis is not, yet, agreed on.

### Diagnosis and Differential Diagnosis of Cerebral Palsy

#### Positive Diagnosis

The diagnosis of CP is essentially clinical. The practice parameter jointly developed by the American Academy of Neurology and the Child Neurology Society (Ashwal et al. 2004) suggests the following diagnostic steps: (1) history taking; (2) neurological and developmental examination for the assessment not only of motor but also of cognitive and language development and of behaviour; and (3) neuroimaging.

Neuroimaging, especially MRI, is increasingly playing a decisive role. Cerebral palsy is mainly characterised by brain lesions, which can be identified by MRI in 70–80% of patients and to a lesser extent by brain maldevelopments, which occur in around 10% (see Pathology, Aetiology, Pathogenesis section). The question addressed to neuroimaging is to find evidence for such a lesion or malformation and whether the topography and extent explains the neurological symptoms and the severity of the clinical picture. These questions are addressed above in the Various Types of Cerebral Palsy section.

Electromyography, (EMG) which may shed some light on the mechanisms (Harrison 1988; Kanda et al. 1988), has no place in practical diagnosis except for the exclusion of other conditions that share with CP some weakness or hypotonia.

#### Differential Diagnosis of Cerebral Palsy

An essential diagnostic consideration is the differentiation of progressive versus static neurological disorders, especially
treatable ones, from CP. Spinal cord tumour in the cervical region and slow growing brain tumours should always be excluded (Haslam 1975).

Many metabolic or heredodegenerative diseases run a slow course and their clinical manifestations can mimic all types of CP. Again here, neuroimaging plays a decisive role, as only cases where lesional or maldevelopmental patterns cannot be identified, must give rise to differential diagnostics.

Hypomyelinating disorders may be difficult to differentiate clinically from CP, as development is often primarily disturbed and neurological signs, whether ataxic, dyskinetic or spastic, are usually present. This again stresses the importance of doing MRI early in the diagnostic work-up of a child with developmental delay and neurological signs suggestive of CP. The finding of hypomyelination indicates the need for molecular genetic testing. It is of importance here to note that the diagnosis of hypomyelination relies on white matter signal hyperintensities on T2 weighted images without changes in two MRIs of at least 6 months distance and in a child 2 years of age or more (Schiffmann and van der Knaap 2009).

Hypotonia is a feature common to most early cases of CP but also to different diseases that are not infrequently misdiagnosed as CP. Prader–Willi syndrome is especially likely to be confused with hyperekplexia (see Chapter 5) and may simulate BS-CP; but there is progressive improvement and touch stimuli frequently produce a considerable hypertonic response with apnoea. The same applies to congenital myotonic dystrophy (Chapter 26), which indeed may coexist with actual hypoxic encephalopathy due to early asphyxia resulting from respiratory muscle involvement (Rutherford et al. 1989).

Hypertonia, which is a common early feature of several forms of CP, may also occur in infants with other problems or in otherwise typical infants (PeBenito et al. 1989). Neck extensor hypertonia in particular is often a precursor of CP (Amiel-Tison et al. 1977; Ellenberg and Nelson 1981). Trouwen and Hadders-Algra (1983) found this to apply only when other abnormalities were associated with hypertension of the neck and trunk. In this respect, it has to be stressed that hypertonia or opisthotonic posturing as an early sign of severe CP is associated with marked developmental delay. Thus, hypertonia in a child with normal early developmental milestones is usually not indicating CP.

DIFFERENTIAL DIAGNOSIS OF BILATERAL SPASTIC CEREBRAL PALSY

Dopa-responsive dystonia usually differs in its age at onset, initial normal development, normal imaging and fluctuating course. But it may resemble mild BS-CP in its movement pattern when the onset is early, as diurnal fluctuation may be absent yet. Because atypical cases occur (Nygaard et al. 1994), a trial of L-dopa at the least suspicion and especially when the MRI is normal, is indicated.

The other important differential diagnosis in a child with leg-dominated spasticity are the hereditary spastic paraplegias there are forms which start early and progress slowly. Some forms with early onset are associated with abnormal cognitive development such subtypes caused by SPG (spastic paraplegia genes), 11 or 21. MRI may be abnormal in some forms (hypomyelination in SPG2 or hypoplasia of the corpus callosum in SPB11) (Gasser et al. 2010). Molecular genetics, thus, seems indicated in a child with leg-dominated spasticity which does not respond to L-dopa and has a normal or ‘not CP typical’ MRI.

Older patients with severe intellectual disability and hypotonia may be given a diagnosis of severe BS-CP because the child may be very hypokinetic and contractures may have developed which makes it difficult to positively diagnose hyperactive tendon reflexes and hypertonia. Again, neuroimaging may help to differentiate, as a severe BS-CP usually has a severe lesion or maldevelopment, whereas in severe intellectual disability, MRI may be unspecific.

DIFFERENTIAL DIAGNOSIS OF UNILATERAL SPASTIC CEREBRAL PALSY

The differential diagnosis of US-CP or congenital hemiplegia is not difficult. In the first months of life, the main differential diagnoses include temporary neonatal hemis syndromes and obstetric brachial palsy. The latter can be differentiated by the absence of deep tendon reflexes and of any involvement of the lower limb just by careful clinical examination. Later, pure hemidystonia or athetosis can raise difficult problems. Indeed, a mixture of dystonic and spastic signs is more common than either alone.

ACQUIRED HEMIPLEGIA

Acquired hemiplegia can result from multiple causes. Cases of acute onset can result from inflammatory disorders, demyelinating diseases, migraine, trauma and, especially, vascular disease and the so-called hemiconvulsion-hemiplegia-epilepsy or HHHE syndrome (Gastaut et al. 1960; Auvin et al. 2012) or acute postconvulsive hemiplegia (Okuno 1994). Cases of progressive onset mainly suggest neoplastic disease, especially gliomas of the brainstem, basal ganglia or thalamus and degenerative disorders (Chapters 10 and 14).

Although acquired hemiplegia can occur at any age, the vast majority of cases start during the first 3 years of life. The onset is often acute and dominated by the features of the causative illness such as convulsions and coma. The hemiplegia is generally maximal from onset and flaccid with marked facial involvement. Spasticity develops later in most cases. Aphasia is present in left-sided cases, in contrast with congenital hemiplegia (Rapin 1995). The degree and rate of recovery are quite variable, some patients being left with severe, persistent weakness, while others make an almost complete recovery. The cause of hemiplegia largely determines the prognosis. Post-epileptic hemiplegia has a bleak outcome, with 75%
of patients developing residual epilepsy and more than 80% having some degree of cognitive impairment (Aicardi et al. 1969; Aicardi and Chevrie 1983). Children with post-epileptic hemiplegia exhibit a characteristic sequence of predominantly unilateral hemispheric edema, followed by global atrophy of the affected hemisphere, which is a virtually specific finding (Kataoka et al. 1988; Aicardi 1994). Vascular hemiplegia has a more favourable prognosis dependent on the extent of the underlying infarct.

Acquired hemiplegia may be difficult to distinguish from US-CP when it occurs in infants, especially as seizures may reveal a previously unrecognised deficit. Flaccidity and facial involvement are strong arguments in favour of an acquired hemiplegia.

Acquired hemiplegia resulting from vascular disease, especially arterial thrombosis or embolism, is dealt with in Chapter 15.

DIFFERENTIAL DIAGNOSIS OF DYSKINETIC CEREBRAL PALSY

The differential diagnosis of dyskinetic CP includes degenerative and metabolic conditions. Genetic dystonias of early onset may be difficult to differentiate and a normal MRI in a dyskinetic movement disorder should give rise to molecular genetic diagnostics. Glutaric aciduria type I usually has a sudden onset following an infectious episode but can also evolve in a slow, progressive way, but usually after a primary normal development (Gascon et al. 1994). Rarer metabolic conditions (e.g. molybdenum cofactor deficiency), may be a cause. Complicated forms of spastic paraplegia with dystonia may raise difficult problems (Fletcher and Marsden 1996). Dopa-responsive dystonia when starting early rather mimics mild BS-CP as described above. Transient dystonia may occur in apparently normal infants during the first year of life (Willemsen 1986; Deonna et al. 1991). It usually affects one or more limbs, does not involve the trunk or neck, presents after 4 months of age and interferes relatively little with the child's activities. The limb posturing may be intermittent or permanent and disappears in weeks or months. A form involving the trunk has been tentatively attributed to maternal cocaine use (Beltran and Coker 1995). A paroxysmal form has been described (Angelini et al. 1988). Transient dystonic attitude limited to the foot may simulate dystonia (Newman et al. 2006).

DIFFERENTIAL DIAGNOSIS OF ATAXIC CEREBRAL PALSY

Ataxic CP should not be confused with physiological incoordination of young infants or of children with global delay of milestones. Simple clumsiness may be responsible for diagnostic errors (Gubbay 1985). The most difficult differential diagnosis is with the progressive ataxias and this problem may take a long time to clarify as some of the progressive cerebellar ataxias may start early and have a very slow course (Gasser et al. 2010). A neuromuscular disease with still normal tendon reflexes may give rise to a misdiagnosis of ataxic CP. Thus, it seems important to stress that low tone is not the qualifying symptom for ataxic CP; other signs such as, for example, disturbed balance beyond of what could be explained by weakness, or over- or undershooting of goal-directed movements are necessary to give the diagnosis.

DIAGNOSTIC DIFFICULTIES AND EARLY DIAGNOSIS

As discussed above, the diagnosis of CP is a clinical one. Consequently, because the typical clinical picture becomes clear only over time, early diagnosis may be difficult. The correct diagnosis of CP is highly dependent on knowledge of normal development and its variants. It is relatively easy to exclude the diagnosis of CP early if the developmental pattern of a suspected infant is normal.

Prechtl et al. (1997) developed an early diagnostic system for the diagnosis of CP that evaluates video-documents of spontaneous neonatal and early infantile movements. A repeatedly documented occurrence of writhing movements and the lack of development of fidgety movements during the first 3 months were reported to be a sensitive and specific sign for the development of neurological abnormalities, which were in the majority CP, but also the development of intellectual disability or minor neurological signs.

Abnormal neurological signs may be transient, so asymmetries of posture and tone, hyperexcitability and hyper- or hypotonia may be found in infants with normally acquired developmental milestones in whom no brain abnormality can be demonstrated. Such features are transitory in over 90% of patients (Michaelis et al. 1993). Transient dystonia occurs in some apparently normal infants during the first year of life (Willemsen 1986; Deonna et al. 1991). It usually affects one or more limbs, does not involve the trunk or neck, presents after 4 months of age and interferes relatively little with the child's activities. The limb posturing may be intermittent or permanent and disappears after weeks or months. Such transient anomalies may be the cause of overdiagnosis of CP and be responsible for the description of children who 'outgrow cerebral palsy' (Nelson and Ellenberg 1982; Taudorf et al. 1984). However, we are not aware of any positively documented case in which clear neurological signs and MRI findings as described above were associated with normal outcome. Children who start walking on tiptoes when they acquire ambulation may be misdiagnosed as having mild
‘diplegia’. The clinical experience shows that when independent walking is acquired within the normal range, BS-CP is highly unlikely as even mild forms of BS-CP are delayed in learning to walk independently. It is also useful to ask whether the child has used a baby walker, as to some extent these induce tiptoe walking.

Such figures indicate how much the diagnosis can err if infants are not followed up and how one should be careful in evaluating the ‘effect’ of early intervention. For this reason, it is generally agreed that the diagnosis of CP should be tentative before the age of 3 years and that CP registers should definitively accept children when the diagnosis is confirmed at the age of 5 years. Of course, there are clear individual situations, especially when the aetiology is known, where the diagnosis can be established earlier.

The changing clinical picture or features of CP can also be a source of diagnostic problems, especially in choreoathetotic and ataxic CP, in which hypotonia is often an early sign. Dyskinetic CP may be wrongly diagnosed in children who are hypotonic and have stereotyped movements. Infants who later prove to have intellectual disability without CP, and who have early neurological signs such as truncal hypotonia, hyperexcitability and decreased variability of motor patterns, can be misdiagnosed with spastic CP. In most infants with US-CP or hemiplegia, asymmetry of movement usually becomes evident only after 4–6 months, even when the lesion is known.

Neonatal neuroimaging findings play an important role in the early diagnosis and prediction of CP. As indicated in The Various Types of Cerebral Palsy section the correlation between morphology and function, topography of a lesion or malformation is related to neurological signs and functional deficit. Thus, the early identification of a lesion or malformation and its topography helps to predict outcome with respect to CP.

- In a preterm born child at term equivalent age, normal MRI is highly predictive of normal motor development, thus the development of CP is highly unlikely (Sie et al. 2005).
- Normal myelination of the posterior limb of the internal capsule (PLIC) seen on MRI in the neonatal period indicates normal motor development. For example, in a child with haemorrhagic infarction, symmetrical myelination of the PLIC argues against the development of US-CP (de Vries et al. 1999) or after asphyxia with HIE and imaging abnormalities of the deep grey nuclei, a normal PLIC bilaterally predicts normal motor development (Martínez-Biarge et al. 2012) (Fig. 8.13).
- Neonatal cranial US-CP has been extensively studied with respect to outcome: 60–100% of preterm born neonates with cystic PVL are at risk of developing spastic CP; when the cysts are located in the domain of the motor tracts there is a risk of nearly 100% (de Vries et al. 2004; Ancel et al. 2006). The same studies give a risk of 47% and 66% for ICH grade IV (haemorrhagic infarction) and of 28% for ICH grade III; whereas ICH grades I and II are only rarely followed by CP. In a preterm born child, US-CP without abnormal periventricular echogenicity and peri- and intraventricular haemorrhage is predictive of a favourable outcome (van Wezel-Meijler et al. 2011).
Cerebral palsy is not exclusively a motor syndrome as associated or even dominant other signs and symptoms may occur in individual cases. Thus, issues of management concern a very wide range of functions including vision, hearing, speech and language development and intellectual status. All these are the subjects of other chapters in this book and here we largely restrict ourselves to some general principles and a look at current developments in the management of CP.

**TREATMENT AND MANAGEMENT**

**PREDICTION OF MOTOR FUNCTION AND EARLY INTERVENTION**

The development of reliable testing instruments for gross motor function, the Gross Motor Function Measure (GMFM; Russell et al. 2002) has led to the development of prediction bands with which levels of gross motor function in children with CP can be predicted very accurately from the age of 2–3 years (Palisano et al. 1997; Rosenbaum et al. 2002). These prediction bands have an important implication: that treatment or management is not in fact going to substantially change the overall outcome for movement in the child with CP beyond the motor function which can be identified or predicted around the age of 2–3 years. This does not mean that treatment is not helpful. First, neglect of any management of the motor system in the child with CP may lead to undesirable secondary effects such as contractures. Second, effective management of a condition has also to do with support in every day life situations, with acceptance of a dysfunction and with integration despite that dysfunction. The prediction bands also play a role when it concerns parental hopes/expectations that early intervention will improve the long-term prognosis for their child.

There is a continuing debate about how much early ‘treatment’ can affect the outcome. Blauw-Hospers and Hadders-Algra (2005) in a systematic review of the effects of early intervention on motor development evaluated 32 studies with interventions starting between birth and a corrected age of 18 months in infants at high risk of developmental disorders and concluded that there was no clear beneficial effect on long-term motor outcome. Another concept is ‘enriched environment’ for promoting optimal brain injury recovery, which has been put forward following animal studies. Systematic reviews show that environmental enrichment improves cognitive outcomes and to a certain extent also motor outcome in infants at high risk of CP (Morgan et al. 2013). This is supported by the idea that learning in infancy is implicit.

**MANAGEMENT OF CEREBRAL PALSY AND QUALITY OF LIFE**

Discussion on management in CP needs to address a specific aspect related to quality of life. Although children with CP report similar quality of life as their peers, severity of impairment and especially pain is associated with lower quality of life (Dickinson et al. 2007; children were aged 8–12 years). Furthermore, problems with physical health such as bodily pain, not necessarily psychological health, are reported to be clearly related to the severity of gross motor deficits and additional impairments (Beckung et al. 2008). Restricted participation of children with CP was also found to a high degree to be explained by pain and higher impairment (more severely impaired walking, fine motor skills, communication and intellectual abilities) (Fauconnier et al. 2009). Thus, management of a child with CP needs to take into account that pain may be a problem and require special treatment. This underlines that adequate treatment of orthopaedic problems (see Treatment and Management section) is not only of functional relevance but also important with respect to pain. Treatment of pain in childhood and adolescence is also important for the prevention of chronic pain syndromes in adulthood, this concerns all motor severity levels in CP.

**MEETING THE NEEDS OF THE DISABLED CHILD**

The child needs: (1) diagnosis, (2) assessment, (3) treatment, (4) management, (5) care, (6) counselling and (7) periodic diagnostic review and reassessment. In most developed countries, assessments will be carried out in an assessment centre, maybe within a hospital setting although sometimes in separate facilities. Because early diagnosis may be difficult, and diagnosis should be tentative before 3 years of age, this will often mean that there is a painful pause for the parents while it is being confirmed. Blood tests may need to be carried out to exclude progressive diseases such as some metabolic disorders. Genetic testing may also be important at this time. But often brain damage has been clearly identified by imaging and a diagnosis has to be conveyed to the parents. Disclosure of a diagnosis of chronic illness in their child is obviously deeply disturbing to the family and the process needs to be carried out sensitively. Good guidelines about disclosure are contained in a booklet provided by the UK charity Scope (Leonard 1999).

Assessment on follow-up relies on four domains: physical, neurological, developmental and sociomedical.
PHYSICAL ASSESSMENT

Any child with CP needs regular assessment of his or her general health status. Upper respiratory tract infections are just as common, or may be more common, in children with CP as in the typical population. In a child with severe motor disability, a lack of mobility may enhance an upper respiratory infection and poor swallowing; a weakened cough reflex may contribute to the development of pneumonia. It is important to counsel with respect to vaccination; CP is not a condition associated with reduced immune competence, and vaccination is of high importance as infections may easily become severe in a child with severe motor disability and lack of mobility.

Anthropometry is important in any child, but especially important in a child who may develop CP. Head circumference indicates normal or abnormal brain growth, which is important where there is a history of brain lesion. In a child with neonatal intracranial haemorrhage, head circumference is important to monitor as hydrocephalus may develop. Children with CP often experience disturbances in growth; many have feeding difficulties and every care has to be taken to maintain adequate nutrition bearing in mind that their basal metabolic rates may be different to those of children without disabilities (Sullivan and Rosenbloom 1996). Many children with CP and severe disability have difficulties with feeding and insufficient intake. Feeding may take a longer time which reduces time for other activities. Forced feeding in a child with swallowing difficulties risks aspiration which can be the cause for repeated pneumonias. In such situations treatment options include a percutaneous gastrostomy.

Contractures and reduced joint mobility are frequent in children with CP, especially those who are non-ambulatory. The ankles (contractures in fixed equines position), the hips (subluxation or luxation) and the spine (scoliosis) have to be regularly monitored (see also hip surveillance in the Orthopaedic Management section). Children with US-CP may develop shortening of both upper and lower limb but predominantly the lower.

Osteoporosis is a frequent problem in immobile patients with CP (GMFCS IV and V), in these the surveillance of osteodensity and prevention of osteoporosis is important (see also Feeding).

DEVELOPMENTAL ASSESSMENT

Development, especially motor, is often delayed and milestones may (e.g. walking) or may not be achieved; the planning of a management programme relies on knowing what exactly the child is able to do. Thus, assessment of the child involves comparing function in all aspects of development with the expected norms for the age (Bax et al. 1990; Michaelis et al. 2013). By the age of 2–3 years future ambulatory ability can be predicted as stated above with around a 90% accuracy.

SOCIOMEDICAL ASSESSMENT

The diagnosis of CP carries the message of a lifelong impairment, often not only with respect to motor, but also to other functions. Thus, good management requires that families receive counselling very early on with respect to support systems that are available. These vary from country to country; while in one country special kindergartens and schools are established others try to integrate children with disabilities into regular institutions. Sociomedical assessment has to take into account the welfare of the entire family, for example, siblings may experience a certain ‘neglect’ as most attention is given to the disabled child.

NEUROLOGICAL ASSESSMENT

Neurological features are described in the section on CP subtypes and the problems of early diagnosis are highlighted.

A specific technique that has been developed over the last decades and helps in assessing a child with a motor problem is the gait laboratory (Van Gestel et al. 2011). Here a videotape, EMG and force plates allow one to study objectively the origins of the child’s abnormal gait. Sutherland and co-workers made standardised measures of normal gait in children (Sutherland 1984; Sutherland et al. 1988) and these have been very helpful in identifying abnormal gait in children with CP. In resource poor countries where such high-tech equipment is not available, simple ways of measuring and recording gait have been used (Law and Minns 1987).

TREATMENT AND CARE ISSUES

When a health professional talks about treatment, the patient and their family may assume that the health professional is talking about a cure. In the early years parents may believe that the child will become ‘normal’. While as indicated below some aspects of the child’s condition can be effectively managed, there are many others where problems will persist. It is important, therefore, to discuss with the family and also, when possible, with the child, that what can be offered is a management programme that can ameliorate the condition and allow the child to develop the best possible function and participation.

As CP is mainly of lesional origin, it is logical to look for prevention or restoration of lesions. Research in neonatology and neurology on neuroprotection has been very active for decades, besides basic research numerous clinical trials have been performed. The only concept which could clearly show improved outcome and which has, thus, been introduced into routine care in neonatology intensive care is hypothermia in the term-born child following asphyxia and hypoxic–ischaemic encephalopathy (HIE). Three positive randomised controlled trials of moderate hypothermia for term infants with hypoxic–ischaemic encephalopathy HIE showed that moderate hypothermia within 6 hours of asphyxia improved survival without CP or other disability by about 40% and reduced death or neurological disability by nearly 30% (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009).
MANAGEMENT OF MOTOR DISORDERS

The following sections centre on physiotherapy, surgical (largely orthopaedic) management, and drug treatments. In general, most of the treatments relate to the spastic form of the disorder; dyskinetic problems are mentioned separately.

Physiotherapy

Many therapists use particular systems of therapy to treat (or manage) the child with CP. The best known (and probably the best thought out) are the techniques developed by the Bobaths (Semens 1967; Bobath 1980; Bobath and Bobath 1984) but there are many other systems of therapy including those of Vojta (1984) and the Pető School (Hári and Ákos 1971). A danger with some of these systems of therapy (such as those advocated by Doman and Delacato – see Cummins 1988) is the great strains they place on the family, disrupting the normal pattern of family life (McConachie et al. 1997).

In recent years the American Academy of Cerebral Palsy and Development Medicine has had working parties reviewing many of these systems and published reports on them. In general, these have failed to find that these systems of therapy are effective, and despite the enthusiasm their use is diminishing with the emphasis being on evidence-based methods being used. Thus the Butler and Darrah (2001) report on the neurodevelopmental treatment (NDT; based on the Bobath method) cast doubt on the value of this method of treatment. However, it should be noted that while orthodox medicine has in recent years been largely converted to the importance of evidence-based medicine, many physical therapy approaches are still widely promoted and parents may still embrace claims that the child can be ‘cured’. The emphasis now is on the prevention of contractures and deformities and on efforts to see that practical functions such as standing, walking and eating are developed and that participation becomes possible. The therapist will therefore look at the child together with the parents and other members of the team and produce a programme aimed at preventing abnormal patterns of behaviour developing and providing a management programme that will help the child to achieve their optimal development.

A certain feature of management of the child with CP that has changed in recent years and that is the emphasis on the value and importance of helping the child’s mobility and access to the environment and participation. An initial study in this regard was that of Butler (1986) emphasising the importance of stimulating the child whose movement capacity limits his or her ability to explore the environment. All the data herald a long overdue positive approach to the strengthening of the child’s motor system in CP and the abandonment of older theories of therapies attempting to change the basic neurological pattern (Damiano 2004).

The levels of evidence for physiotherapy interventions, particularly strengthening and to a lesser extent functional training, in school-aged children with CP has improved in recent years. A systematic review focusing on the common conventional physiotherapy interventions used with children with CP, aged 4–18 years, included strength and functional training, weight-supported treadmill training and neurodevelopmental treatment (Martin et al. 2010). Strength training was the most studied intervention with significant improvements found in the strength of selected muscle groups using dynamometry, some studies also showed significant improvement in function. Functional training showed improvements in gross motor function, endurance and temperospatial measures, such as gait speed and stride length. Nonsignificant trends of improvement on the GMFM and gait velocity were found for treadmill training by a few studies with low levels of evidence (case series). Of three studies that evaluated neurodevelopmental treatment, one high-level evidence study, that is, randomised controlled trial, found significant improvements on the GMFM. All studies reviewing treatment dosage, yet found no significant differences for different intensities of treatment.

Constraint-Induced Movement Therapy

Constraint-induced movement therapy (CIMT) has been developed in adult stroke patients where the unaffected limb is constrained, requiring the patient to attempt to use their partially inactive limb. It has proved effective for these patients and its use has been extended to children, particularly those with US-CP. A recent systematic review and meta-analysis (Tinderholt Myrhaug et al. 2014) summarised the effects of CIMT on hand function and functional skills and supported the existing evidence that CIMT improves unilateral hand function and functional skills. However, in a majority of the included studies, equal improvements were identified between intensive intervention and conventional therapy or between two different intensive interventions. The authors concluded that different types of training, different intensities may have contributed to the observed variations in the effectiveness of CIMT.

Another factor may contribute to these variations: many children with US-CP due to early unilateral brain lesions control their paretic hands via ipsilateral corticospinal projections from the contra-lesional hemisphere (see The Various Types of Cerebral Palsy section). They can be identified by the fact that they show mirror movements of either hand when moving their hand. These patients respond less well to CIMT especially with respect to motor speed than patients with preserved contralateral corticospinal projections (Kuhnke et al. 2008). These differences have also been shown concerning the neuromodulative effects of therapy, as demonstrated by magnetoencephalography, transcranial magnetic stimulation and functional magnetic resonance imaging (Juenger et al. 2007; Walther et al. 2009).

In conclusion, physiotherapy in CP is considered necessary either continuously or in regular, more intensive settings. It is important to note that no system is more effective than another. In the individual patient, choice of a specific system and its intensity will depend on the goal which the treatment wants to achieve and this goal achievement has to be adapted continuously to every day life situations.
Drug Therapy

The two most commonly used drugs in CP are botulinum toxin and baclofen.

The background to the use of botulinum toxin goes back to the work of Tardieu et al. (1972) who reported that alcohol or phenol injections into spastic muscles decreased spasticity by blocking the release of acetylcholine at the neuromuscular junction. Long-term results were, however, debatable. With the introduction of botulinum toxin there has been a great increase in attempts to reduce spasticity by this means. Early papers of Cosgrove et al. (1994) and Corry et al. (1997) with reasonable trials in both upper and lower limbs have lent quite powerful support to its use as an adjunct to other forms of management of the motor disorder. Botulinum neurotoxin type-A (BoNT-A) has been used in association with other interventions in the management of spasticity in children with CP now for almost two decades. A consensus statement based on an extensive review of the literature (Love et al. 2010) concluded that injection of BoNT-A in children with CP is generally safe although systemic adverse events may occur, especially in children with more physical limitations (GMFCS V). The committee further concluded that injection of BoNT-A is effective in the management of lower limb spasticity in children with CP and when combined with physiotherapy and the use of orthoses, these interventions may improve gait and goal attainment. But it was also stressed that assessment of children with CP and evaluation of outcomes following injection of BoNT-A are complex and therefore, a range of measures and the involvement of a multidisciplinary team is recommended.

Baclofen orally has been used in CP for a long time and it can be an effective muscle relaxant. It often has to be used in relatively high doses and the consequent side effects, particularly of sleepiness, urinary retention and gastrointestinal problems, may be significant. In these situations, the use of baclofen intrathecally, giving the drug by continuous infusion or in boluses (Armstrong et al. 1997) can be helpful. It is recommended especially in severe BS-CP, where stiffness may make it difficult for the child to be nursed and managed, and may be very effective also in reducing pain. There is evidence from non-randomised, controlled trials to support the effectiveness of intrathecal baclofen infusion for the short-term reduction of severe spasticity in patients who are unresponsive or cannot tolerate oral baclofen, and evidence from observational studies with controls, for the long-term reduction of severe spasticity (Health Quality Ontario 2005).

Orthopaedic Management

It has already been mentioned that many contractures and the abnormal growth of muscles and hence joints may be prevented by early postural management, helped by splinting to maintain joints in their neutral position. The management of this will be the responsibility of both the orthopaedic surgeon and a physical therapist.

- With respect to hip(sub)luxation, a prospective study of hip surveillance programme in Sweden did impressively show that, by systematic monitoring and soft tissue surgery, luxation can be successfully prevented in near to 100% of participants (Robb and Hägglund 2013). This programme has now been introduced in several other countries in Europe.
- Probably the commonest orthopaedic procedures are carried out around the ankle to address problems of equines position and tightening of the Achilles tendon. In a first step the feet are supported by an orthosis for the correction of dysfunctional posture; predominant hypertonicity of the extensor muscles may be modulated by botulinum toxin injection; in the case of fixed contractures operative correction may become necessary.
- Scoliosis management is usually done in a combination of physiotherapy and adapted support for the sitting position. Surgical treatment may become necessary in single cases and requires an interdisciplinary approach: the paediatric pulmologist to assess lung function, the paediatric neurologist to evaluate the global situation and functioning and the orthopaedic surgeon with specific expertise in scoliosis surgery.

Specific Surgical Approaches

Dorsal rhizotomies were considered in the 1970s but were not performed for many years until Peacock and Arens (1982) initiated the use of this form of therapy again. In selective dorsal rhizotomy (SDR) a partial sectioning of the dorsal roots from L2 to S1 is performed. SDR can be performed where the nerve root exits the intervertebral foramina via multi-level laminotomies, or at the level of the conus via a single-level laminotomy; outcome is reported similar (Ou et al. 2010). Functional improvement and good levels of satisfaction with life habits has been demonstrated as much as 17–26 years later (Langerak et al. 2011). In a meta-analysis of three randomised controlled trials of patients treated with SDR combined with physical therapy or with physical therapy alone, McLaughlin et al. (2002) found that 9 months to 2 years after SDR, there was a significantly greater improvement in the gross motor function abilities in the group treated with SDR and physiotherapy. A recent systematic review of 52 studies found that selection criteria for SDR vary considerably (Grunt et al. 2014). A certain consensus concerns two indications: children with BS-CP, who can walk and have spasticity mainly in the legs, for example, the typical diplegia of the preterm. As discussed in the Prevalence section, this form of CP is decreasing, which also explains that dorsal rhizotomy is less often performed. A second indication is severe spasticity in the legs with pain and difficulties in every day handling which does not adequately respond to drug treatment.
Other Aspects of the Motor Disorder

The above discussion about management of the motor disorder largely relates to the spastic forms of CP. In patients with dyskinetic CP, contractures and fixed deformities are not usually a problem (although they do occur). The main difficulties relate to the involuntary movements and dystonic posturing. Sometimes this can be very powerful and extremely difficult to interrupt, making all purposeful movement impossible. The following drugs may be used, but success is difficult to predict and individual trials are recommended.

- **Dopamine** may be effective, it is important to introduce the drug slowly because of the risk of side effects.
- **Trihexyphenidyl** may be used together with dopamine, then in a low dose, or alone.
- **Tetrabenazine** is another possibility, although in off-label use.
- **Baclofen** - severe dystonic CP may also respond well to a baclofen pump.

A particular problem in CP is **drooling**, which may occur in as many as 50% of patients. It is an unpleasant problem and difficult to treat. Various drugs have been tried, of which scopolamine patches are probably the most easy to use as effect and tolerability can be judged immediately (Lewis et al. 1994). Benztropine and glycopyrrolate are orally administered drugs. BoNT-A can be used injected into salivary glands, either into the parotis which is responsible for the pulsatile excretion of saliva during meals or rather into the submanibular glands, which also excrete between meals and thus, are probably mainly responsible for the drooling. redirection of the salivary ducts and removal of the salivary glands is another possibility that is reported to have good rates of success in experienced hands (Burton 1991). A Cochrane database review (Walshe et al. 2012) evaluated the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with CP. The authors found six trials, meeting their quality criteria, four using BoNT-A and two were trials on the pharmacological interventions, benztropine and glycopyrrolate. No randomised controlled or controlled clinical trials were retrieved on other forms of intervention. All studies showed some statistically significant change for treatment groups up to 1 month post intervention. However, methodological flaws did not allow conclusion on the effectiveness and safety of either intervention.

**FEEDING**

It is curious that older textbooks on CP (Ingram 1964) make no mention of feeding problems in the child. In fact a very large proportion of children with CP have feeding difficulties. These often persist through into adult life. In moderate to severe CP something like 15% of young adults may have a gastrostomy (Eltumi and Sullivan 1997). Difficulties occur early and need to be recognised so that the child does not suffer from inadequate nutrition, which may have an effect on the developing brain. A child with CP may never develop beyond the suck-swallow pattern of feeding and never be able to chew. Cerebral palsy clinics and child development centres now have specialist feeding clinics with dieticians, speech therapists and physicians as part of a team trying to maintain adequate nutrition and a satisfactory feeding pattern. Better feeding together with putting weight on skeletal structures is important for the prevention of osteoporosis and bone fractures. It is important to remember that apart from a nutritional role, mealtimes are significant social occasions in most societies and it is desirable that the child should not be isolated by being fed away from the rest of the family (Sullivan and Rosenbloom 1996).

**Speech/Communication**

Communication is highly dependent on the ability to speak. Children with CP often have speech difficulties. This is because, on the one hand, they have severe intellectual disability and do not learn to understand language and to develop a speech concept. On the other hand, the neurological features in CP may be so extensive as to also affect the articulatory motor domains, which can result in dysarthria or even anarthria, so that speech production is incomprehensible or not possible although the affected children do understand language. This is especially seen in children with dystonic CP and in the severe forms of BS-CP. As it seems important to have a tool to describe the speech performance of children with CP in a reliable way which is easy to use by doctors, therapists and also care givers, the SCPE network has compared different tools and suggests the Viking Speech Scale as a reliable, easy to use tool which can be applied through direct observation of children or through case note review (Pennington et al. 2013).

**ADOLESCENCE AND ADULT LIFE**

It is beyond the scope of this book to discuss the issues that arise as the child with a disability gets older. Briefly, it is important to know that severity of motor and additional impairment is the main factor determining long-term survival of children with CP and after the first years the expectation of life for people with CP is not substantially lower than that for the normal population; for example, around 90% of those who were alive at 2 years become 20 years and older (Hemming et al. 2005). Often services that have been provided by paediatricians or paediatric neurologists fall away and young people find themselves in the community without a dedicated health service (Thomas et al. 1989). The tasks for the adolescent include the achievement of independence, self-image and identity, the expression of sexuality and vocation. The word vocation rather than work is used deliberately because for many of these young people open employment may be difficult to find.
situation may have to be faced that the young person is not going to have a job but nevertheless needs to have a purposeful life plan. For the family this is often a difficult period. The parents/carers are becoming older and if their child is severely disabled they may begin to realise that the care that they have formerly lavished on the child may not be possible in the future. Provision for where a young person with severe disabilities can spend adult life vary considerably from country to country and is often unsatisfactory.

REFERENCES


PART IV

Metabolic and Heredodegenerative Disorders

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# Metabolic Diseases

_Linda De Meirleir_

## Disorders of Subcellular Organelles

### Lysosomal Diseases

- Sphingolipidoses
- Gangliosidoses
  - GM1 Gangliosidosis
  - GM2 Gangliosidoses
  - Gaucher Disease
  - Niemann–Pick Disease A and B
  - Fabry Disease
  - Ceramidosis (Lipogranulomatosis, Farber Disease)
  - Mucosulfatidosis (Multiple Sulphatase Deficiency, Austin Disease)

### Mucopolysaccharidoses

- MPS IH (Hurler type)
- MPS IH (Scheie type)
- MPS II (Hunter Disease)
- MPS III (Sanfilippo Disease)
- MPS IV (Morquio Disease)
- MPS VI (Maroteaux-Lamy Disease)
- MPS VII (Sly Disease)

### Mucolipidoses

- Sialidosis I (Cherry-Red Spot Myoclonus Syndrome)
- Mucolipidosis IV

### Oligosaccharidosis and Sialic Acid Disorders

- Salla Disease
- Aspartyl-Glucosaminuria
- Alpha-Mannosidosis
- Beta-Mannosidosis
- Fuccosidosis
- Galactosialidosis

### Congenital Disorders of Glycosylation

### Peroxisomal Disorders

- Peroxisomal Biogenesis Disorders
  - Zellweger Spectrum Disorders
  - PTS2-Related PBD: Deficiency of PEX7 and PEX5L
  - Disorders of Peroxisomal Fission

- Disorders of Peroxisomal Enzyme Deficiencies
  - Deficiencies of the Peroxisomal b-Oxidation
  - Deficiency of a-Oxidation: Adult Refsum Disease
  - Deficiency of Ether-Phospholipid Synthesis
  - Deficiency of Glyoxylate Detoxification
Disorders of Amino Acid and Organic Acid Metabolism

Phenylketonuria and Hyperphenylalaninaemia

Tetrahydrobiopterin (BH4)

Maternal Phenylketonuria

Tyrosinaemia

Disorders of Branched-Chain Amino Acid Metabolism

Maple Syrup Urine Disease

Isovaleric Aciduria, Propionic Aciduria and Methylmalonic Aciduria

Intermittent and Late-Onset Forms

Chronic Progressive Forms

Other Diseases in This Pathway

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Metabolic Diseases

Linda De Meirleir

The number of inborn errors of metabolism is extensive, and more than 600 entities have been recognised. Most of these diseases are rare. As a consequence, it is difficult for physicians taking care of adults or children to have a readily available knowledge of all clinical syndromes and their biochemical and genetic basis as well as their treatment possibilities. It is useful to describe screening procedures that can help in the initial identification of patients with inborn errors of metabolism.

Many symptoms prominent in patients with inborn errors of metabolism are often nonspecific and can be caused by more common conditions, such as infections or asphyxia. These conditions are usually easier to diagnose; therefore, their differential diagnoses should always be considered first.

It is necessary that each physician assessing a child with unexplained symptoms and signs thinks of the possibility of a metabolic disease and further investigates the case. This will be done initially with the indicated screening methods and further with a specific diagnostic work-up, in collaboration with a specialist who has a broad knowledge of available laboratory tests and who can help select the ones that lead to an exact diagnosis.

Progress in the molecular understanding of these disorders has revealed the clinical heterogeneity of some metabolic diseases. This important variability in the clinical syndrome caused by a specific metabolic abnormality can be apparent even among affected members within the same family. It is important to be aware of this complicating aspect, as the family history is used as one criterion for the identification of an inborn error of metabolism. To further complicate matters, affected family members sometimes develop symptoms later in life such as in adolescence or adulthood.

Most inborn errors of metabolism affect the nervous system. For many of these diseases little is known about the exact pathogenic mechanism by which the metabolic deficit generates the central nervous system (CNS) anomalies, including the dysmorphogenesis that is often present. Energy deficiency or toxic effects from the storage of certain metabolites leading to neuronal death are possible explanations, but exactly which processes are involved is often far from clear.

Several diseases can now be diagnosed using specific biochemical assays performed on specific tissues to reveal the enzymatic deficit. With the advances in molecular biology, corresponding gene mutations often can be identified and eventually can be used for further family testing and prenatal counselling. Sometimes, one is restricted to a biochemical diagnosis when the gene involved is not yet fully characterised or is too cumbersome to analyse, as can be the case for very large genes. In other cases, the opposite is true, and it is easier to document a specific mutation than to do the biochemical assay. More and more, use of gene panels in specific groups of metabolic diseases and next generation sequencing is used early in the diagnostic evaluation leading to a number of new diseases over recent years. However, clinical phenotyping is necessary in order to make the right interpretation of genetic data.

Most inborn errors of metabolism are inherited in an autosomal recessive mode. In most of these cases, the disease can only manifest itself fully in homozygotes for the mutation. This is generally a rare occurrence, except in consanguineous families. However, some inborn errors of metabolism are caused by mutations in genes located on the X chromosome, and the disease is then called ‘X-linked’. The effect is two-fold: first, the disease becomes dominant in male offspring inheriting the mutation; second, because of variable random X chromosome inactivation in various tissues, the expression of the disease can be highly variable from one tissue to another and from one girl to another. Few inborn errors of metabolism are autosomal dominant or arise de novo. Finally, subsets of the respiratory chain genes that are encoded within the mitochondrial DNA are only maternally inherited. Treatment possibilities include special diets, enzyme replacement therapy, stem cell transplantation, specific cofactors or other substances. Early diagnosis can be life saving in some conditions.

DISORDERS OF SUBCELLULAR ORGANELLES

LYSOSOMAL DISEASES

The function of the lysosome is to hydrolyse a large number of complex molecules. When this function fails, storage within the lysosomes in different organs is the result. Most lysosomal diseases are due to a genetic defect of one of the lysosomal enzymes involved in the degradation of a specific substance. However, some diseases, including mucolipidoses II and III,
result from post-traductional abnormalities affecting normally synthesised proenzymes. Others (e.g. Salla disease and cystinosis) are due to defective transport of substrates across lysosomal membranes.

All lysosomal diseases are inherited as recessive – mostly autosomal recessive traits.

The clinical presentation and phenotypic manifestations of the same defective enzyme are variable, reflecting the possible existence of multiple different abnormalities of the same gene and/or occurrence of joint effects of other genes, alternative messenger RNA splicing, or post-traductional modifications.

**SPHINGOLIPIDOSES**

The sphingolipidoses are lysosomal diseases with absent or imperfect degradation of the sphingolipids, which are essential components of CNS membranes. The major steps of sphingolipid catabolism and the corresponding enzymes and enzymatic blocks are represented in Figure 9.1.

**GANGLIOSIDOSES**

These are important diseases that result from enzymatic blocks involving the removal of N-acetylgalactosamine from the complex ganglioside molecules. Gangliosides are found mainly in nuclear areas of grey matter and less in the white matter. Although many gangliosides have been isolated from the brain, four major components, GM1 to GM4, account for over 90% of the total ganglioside fraction.

**GM1 Gangliosidosis**

This group of disorders is caused by deficiency of acid beta-galactosidase, the gene is located on 3pter–3p21. In addition to lipid storage closely similar to that in the GM2 gangliosidoses,
Chapter 9  Metabolic Diseases

the stored material also includes vacuolar inclusions with accumulation of numerous mannose-containing oligosaccharides, resulting from defective terminal beta-galactose residue removal during glycoprotein catabolism. Several beta-galactosidase isoenzymes are recognised. GM1 deficiency can also present as a nonimmune fetal hydrops. The severity of the phenotype is proportional to the degree of residual enzyme activity (Brunetti-Pierri and Scaglia 2008).

The three isoenzymes (A1, A2, A3) are defective in all forms of GM1 gangliosidosis, and the various phenotypes are probably explained by mutations resulting in proteins with different residual substrate specificities (Suzuki et al. 1991, Lyon et al. 2006). Beta-galactosidase is involved not only in the degradation of GM1 but also in other galactose-containing oligosaccharides and keratan sulphates. Deficiency of beta-galactosidase can therefore also result in Morquio B (MPS type IV B) or can be involved in galactosialidosis.

**GM1 gangliosidosis type 1** (pseudo-Hurler disease) is a rare autosomal recessive disease, clinically present at birth or even prenatally (Tasso et al. 1996). Affected infants are markedly hypotonic, suck poorly, fail to thrive and do not make any psychomotor progress. They have frontal bossing, coarse facial features, oedema, gum hypertrophy, macroglossia and hirsutism. Half of them have a retinal cherry-red spot, and hepatosplenomegaly is usually evident. The skeletal deformities are similar to those of Hurler syndrome. The course is severe. Blindness and deafness, quadriplegia and epileptic seizures appear, and death usually supervenes before 2 years of age.

**GM1 gangliosidosis type 2** has a later onset: between 6 months and 3 years of age. No marked skeletal abnormalities are present, although the first or second lumbar vertebrae are abnormally shaped, so that the presentation is one with developmental delay, then regression with pyramidal, cerebellar and extrapyramidal signs (Sandhoff and Harzer 2013). Optic atrophy and a cherry-red spot may be present, and acoustic startles occur in half of the cases although usually late in the course. The gene is the same as for type 1 but there is heterozygosity for two separate mutations.

**GM1 gangliosidosis type 3** (so-called adult type) is rare. Onset may be in childhood or adolescence with abnormal gait and worsening speech. The presentation is variable; dystonia and parkinsonism are frequent (Roze et al. 2005). A picture of spinocerebellar degeneration is possible. Variants include a dystonic form (Tanaka et al. 1995) and atypical cases, for example with myopathy and cardiomyopathy. Intellectual deterioration may be late or absent in such forms. Low T1 signal from the pallidum and putamen has been reported (Tanaka et al. 1995), and a leukoencephalopathy is present (van der Voorn et al. 2004).

The diagnosis of GM1 gangliosidosis is characterised by absence or presence of small amounts of urinary excretion of keratan sulphates and increase of oligosaccharides; the presence of bony abnormalities, especially of the lumbar vertebrae, and the presence of foamy cells in the bone marrow. Vacuolated lymphocytes may be found in the peripheral blood and foamy histiocytes in the bone marrow.

It is confirmed by the absence or marked reduction of beta-galactosidase activity in leukocytes or fibroblasts. In the late (type 3) forms, beta-galactosidase deficiency is partial (5–20% normal). Prenatal diagnosis can be made on cultured amniotic cells or trophoblasts.

**TREATMENT IN GM1 gangliosidosis**

The use of iminosugar inhibitors of glycosylceramide transferase that are effective in Gaucher disease has been tried in other glycosphingolipid disorders (Aerts et al. 2006). Other chaperone therapies might be promising such as NOEV (N-octyl-4ep-B-valenamine) acting as a competitive inhibitor of beta-galactosidase and a chemical chaperone to restore enzymatic activities in somatic cells from patients with GM1-gangliosidosis (Suzuki 2013). So far, there is no definite cure for this disease.

**GM2 Gangliosidoses**

GM2 gangliosidoses are the commonest diseases of this group. Several varieties are known depending on the nature of the enzyme. Three isoenzymes of hexosaminidase have been recognised.

Hexosaminidase A is composed of one alpha and two beta subunits (A1, B2); hexosaminidase B solely of B units (B1, B2) and hexosaminidase S only of A units (A2). In classic Tay–Sachs disease or B variant, hexosaminidase A (Hex A) and S are inactive as a result of a mutation at the alpha locus on chromosome 15 (15q22–q25.1). Hexosaminidase B is normal but unable to hydrolyse gangliosides in vivo. Different mutations at the alpha locus are known. GM2 gangliosidosis in French Canadians (Palomaki et al. 1995) may be due to a different DNA defect (deletion of intron 1 and promoter region) to that in Ashkenazi Jews which in 73% of cases comprises a four-base insertion in exon 11. However, some French Canadians have the same mutation as Ashkenazi Jews and, within a single population, different mutations can be observed.

The B1 mutation results in an altered substrate specificity of Hex A. In this variant, the mutated enzyme displays essentially normal activity when tested with conventional methyl-umbelliferyl substrates but is unable to hydrolyse GM2 or sulphated methyl-umbelliferyl synthetic substrate. The O variant (Sandhoff disease) is characterised by deficiency of both beta-hexosaminidase isoenzymes A and B due to a mutation at the beta locus on chromosome 5q13. Variant AB is caused by the deficiency of an activator protein (saponin) required for the interaction of HEXA-A with its natural substrate (Cordeiro et al. 2000). There is, thus, a considerable clinical and biochemical heterogeneity among the GM2 gangliosidoses (Lyon et al. 2006).

The pathological changes in the CNS are common to all forms of gangliosidosis, with some variations related to the length of the course and undefined factors. The main finding is the presence in neurons of lipid-soluble material within the cytoplasm, with later disappearance of many neurons and the development of extensive gliosis. Purkinje cells and neurons
in brainstem nuclei, and neurons in visceral plexuses, are also affected.

**Tay–Sachs disease** is by far the most frequent form of gangliosidosis, affecting 1 in 2,000 persons among the Ashkenazi Jewish populations of eastern European background. The gene frequency is estimated to be 1 in 27 among Ashkenazi Jews and 1 in 380 in non-Jews.

The onset is between 3 and 9 months, with loss of acquired milestones and of muscle tone following an essentially normal initial development. Acoustic startles may precede all other symptoms and persist for several months. Neurological symptoms rapidly progress. Initial hypotonia is replaced by spastic tetraparesis, and epileptic seizures may appear late in the course. After the first year of life, the infants are blind and unresponsive and often develop a progressive macrocephaly. Magnetic resonance imaging (MRI) in the early stages of the disease shows increased T2 signal from the basal ganglia. The caudate nuclei often protrude into the lateral ventricles. Later, T2 signal is increased throughout the white matter (Grosso et al. 2003).

Death usually occurs before 3 years of age. From early in the course, a cherry-red spot is present in both macular areas, surrounded by a zone of whitish retina. The whitish zone is due to lipid storage in the retinal ganglion cells that are especially dense in the posterior pole, whereas the red spot represents the normal macula, which is devoid of ganglion cells and appears abnormally red by contrast with the surrounding retina. Although characteristic of Tay–Sachs disease, the cherry-red spot may also be seen in other types of gangliosidosis, in sialidosis, in Niemann–Pick disease, in infantile Gaucher disease and in rare cases of metachromatic leukodystrophy and of Krabbe disease (Chen et al. 2014).

**Sandhoff disease** (type O gangliosidosis) is clinically indistinguishable from classic Tay–Sachs but represents only 7% of cases of GM2 gangliosidosis.

The diagnosis of Tay–Sachs disease is easily confirmed by absence of Hex A or of both Hex A and Hex B in serum or leukocytes. Patients with a B1 mutation have intermediate levels of Hex A activity when tested with a nonsulphated umbelliferol substrate. For them the use of sulphated 4-Mu-gal-N-Ac-6-sulphate (4-MUG) substrate is necessary for diagnosis (Matsuzawa et al. 2003). Prenatal diagnosis by Hex A assay is possible in the second trimester of gestation.

Carrier detection using blood is possible and has been automated for mass screening surveys (Leib et al. 2005). Pseudodeficiency of Hex A occurs in compound heterozygotes who carry one common disease-causing mutation on one allele and one of two benign mutations on the second allele. Such individuals are clinically normal although they cannot hydrolyse synthetic 4-MUG substrates. These benign mutations have significant implications for heterozygote screening programmes and for prenatal diagnosis. Their frequency was found to be respectively 3% and 38% in Ashkenazi Jewish and non-Jewish enzyme-defined carriers (Cao et al. 1993).

**Juvenile GM2 gangliosidosis** is rare. Onset is between 2 and 6 years with gait instability and often speech disturbances, followed by ataxia and pyramidal tract signs. Intellectual deterioration is present at end-stage. Ataxia and dysarthria may be the first manifestation. Seizures may occur and dystonia and choreoathetotic movements have been reported. There is no racial predilection.

**Late-onset GM2 gangliosidosis** (Neudorfer et al. 2005) is also termed chronic GM2 gangliosidosis or ‘adult form’, although the onset is before 10 years in 35% of cases. Onset is with a special form of dystartha followed by gait difficulties, pyramidal tract signs, ataxia and lower motor neuron involvement. Psychiatric disturbances occur later in half the patients. Dystonia is present in some patients, and supranuclear ophthalmoplegia has been reported (Rucker et al. 2004).

Atypical forms may present as anterior horn cell disease of juvenile onset (Drory et al. 2003), as isolated dystonia, or as atypical spinocerebellar degeneration. An unusual presentation mimicking a brainstem tumour has been reported (Nassogne et al. 2003).

A clinical picture of Tay–Sachs disease may be seen in patients with normal amounts of Hex A and B (AB variant) (Cordeiro et al. 2000; Lyon et al. 2006) and is difficult to diagnose as it requires direct study of labelled natural gangliosides catabolism.

The B1 variants usually present as infantile disease but may also be found in patients with juvenile and chronic forms (Grosso et al. 2003), although in the latter type an AB variant may be less rare.

No effective therapy for the GM2 gangliosidoses is yet available. Substrate reduction therapy with the ceramide synthesis inhibitor miglustat has been shown in animals to be partially effective (Andersson et al. 2004; Cox 2005) (see below). However, the process of ganglioside accumulation and consequent brain degeneration is already well established by the mid-trimester of fetal life, so the prospects for enzyme replacement therapy are not favourable.

**Deficiency in lysosomal alpha-N-acetylgalactosaminidase** – Schindler disease – may resemble infantile neuroaxonal dystrophy.

**Gaucher Disease**

Gaucher disease is a relatively frequent recessive disease affecting 1 in 50,000 to 1 in 200,000 persons and 1 in 800 in Ashkenazi Jews (Grabowski 2008). It is due to deficiency of beta-glucocerebrosidase (see Fig. 9.1). Its deficiency results in the accumulation of glucosylceramide in the lysosomes of macrophages. The gene coding for beta-glucocerebrosidase is located on chromosome 1q21–q31. The different types may correspond to allelic mutations at this locus, although other factors are operative as shown by phenotypic differences even for the same mutations. Over 150 mutations are currently known, some with neurological manifestations. It has been proposed that phenotypic variations may be due to compound heterozygosity, which is frequent, or to post-transcriptional abnormalities. Three main phenotypes are encountered:
non-neuronopathic, neuropathic infantile form and juvenile neuropathic type (Sidransky 2012).

**Type 1 Gaucher Disease**

Type 1 Gaucher disease or non-neuronopathic type is the most common type and can start in childhood. It is mainly marked by hepatosplenomegaly, bone abnormalities, and sometimes hypersplenism with anaemia and pulmonary manifestations. There is no involvement of the CNS except in rare cases (Filocamo et al. 2004). However, there is some evidence that subclinical neurological involvement may be detected; for example, by study of saccadic eye movements (Accardo et al. 2005). Glucocerebrosides accumulate throughout the reticuloendothelial system. The major marker is the presence of the Gaucher cell in the bone marrow, spleen, liver and lymph nodes.

**Type 2 Gaucher Disease**

Type 2 Gaucher disease (acute infantile Gaucher disease or neuronopathic type) is also due to glucosylceramide beta-glucosidase deficiency. The clinical onset is at 3–5 months of age with muscle hypotonia, axial hypertonia and loss of interest in surroundings. Spasticity gradually sets in, with neck retraction and bulbar signs becoming prominent and resulting in feeding difficulties. There can be a vertical ophthalmoplegia. Splenomegaly is usually pronounced. Cherry-red spots are sometimes present. Convulsions may occur at age 6–12 months. Death usually occurs before 2 years of age.

**Type 3 Gaucher Disease**

Type 3 Gaucher disease (juvenile Gaucher disease) becomes apparent during the first decade of life, the major features at this period being slowly progressive hepatosplenomegaly, rapidly associated with intellectual disability. Cerebellar ataxia and extrapyramidal signs frequently develop. The most suggestive features include supranuclear horizontal ophthalmoplegia that may be the initial feature, and in some myoclonic epilepsy (Verghese et al. 2000; Frei and Schiffmann 2002). Audiometric studies show that involvement of the auditory pathways is frequent (Bamiou et al. 2001). Moderate bony changes such as widening of humeral and femoral diaphyses may be present. Neurological features are quite variable. Some patients have early features such as ophthalmoplegia starting in the first few years and may keep a normal intellect to adulthood with only extrapyramidal signs without epilepsy or deterioration, and many intermediate forms exist (Lyon et al. 2006).

A phenotypic variant of type 3, known as the Norrbottian type, is frequently encountered in northern Sweden. The onset is early, around 1 year of age, with progressive hepatosplenomegaly and hypersplenism. Cognitive deterioration, ataxia and spastic tetraplegia evolve slowly after age 3 years.

Splenectomy often precipitates appearance or aggravation of neurological signs. This type is regularly associated with a homozygous L444P mutation.

**Diagnosis of Gaucher Disease**

Bone marrow can show Gaucher cells; in serum, elevated levels of chitotriosidase and angiotensin-converting enzyme and increase of acid phosphatase are found.

Defective beta-glucocerebrosidase can be measured in lymphocytes, leukocytes and also on dry blood spots. Further confirmation can be by molecular analysis. Saposin C deficiency due to mutations in the PSAP gene encoding the precursor of saposin A, B, C can have a similar picture (Tylki-Szymańska 2007). In saposin C deficiency glucocerebrosidase activity, however, is normal but the finding of Gaucher cells on bone marrow and striking elevation of chitotriosidase should lead to the molecular analysis of the PSAP gene.

**Treatment in Gaucher Diseases**

*Enzyme replacement therapy* (Grabowski 2005) is highly effective for Gaucher type 1 and for the systemic manifestations in Gaucher type 3. It does not improve neurological signs because the enzyme does not cross the blood–brain barrier, although some improvement might occur in the long term.

Enzyme replacement by imiglucerase, is currently infused every 2 weeks with doses varying between 15 and 60U/kg per infusion. Recently velaglucerase-alfa and taliglucerase were also approved (Zimran and Elstein 2014).

With this treatment the volume of liver and spleen decreases quickly and stabilises; anaemia and thrombocytopenia disappear, painful crises are less and general status improves. Biological markers such as chitotriosidase, acid phosphatase and angiotensin-converting enzyme are useful in the follow-up. There is no evidence that enzyme replacement therapy has influenced the neurological progression even when used in high doses (120 U/kg/2 weeks [Kaplan et al. 2013]).

*Substrate reduction therapy* with imino sugar inhibitors of glycosyl ceramide glucosyl transferase, especially N-butyl deoxygalactonojirimycin (miglustat), the key enzyme in synthesis of glycosyl sphingolipids, has been shown to be effective against the visceral manifestations of the disease, resulting in decrease in size of the spleen and correction of haematological abnormalities (Pastores et al. 2005). It is used as a daily oral therapy (100mg/1.73m² of body surface) three times daily. Its effect is probably less complete than with enzyme replacement. In addition to its substrate reduction effect (Cox 2005), it may also produce a chaperone-mediated stabilisation of mutant beta-galactosidase enzyme. Adverse reactions include weight loss, tremor, and more rarely a peripheral neuropathy, requiring electromyography (EMG) monitoring.
Niemann–Pick Disease A and B

Niemann–Pick disease comprises a heterogeneous group of disorders linked by an accumulation of sphingomyelin in the reticuloendothelial system. Of the three main types A, B and C, types A and B are due to a deficiency of acid sphingomyelinase and constitute a neuronopathic form A and non-neuronopathic form B. Type C will be discussed with disorders of cholesterol metabolism.

Niemann–Pick disease A and B is transmitted as an autosomal recessive character and type A occurs especially in Ashkenazi Jews.

Clinical features of Niemann–Pick disease type A

The clinical onset is during the first year of life, with hepatosplenomegaly and poor physical and cognitive development. Jaundice, diarrhoea and pulmonary infiltrates are common. Myoclonic seizures, spasticity and blindness are the major manifestations. One-quarter of the patients have retinal cherry-red spots. A peripheral neuropathy occurs in 10% of cases, with slowing of conduction velocities. Death occurs before age 5 years.

The diagnosis is suggested by the presence of vacuolated cells in the bone marrow. Sphingomyelinase deficiency can be found in leukocytes or fibroblasts. The diagnosis can be confirmed by molecular analysis.

The gene maps to 11p15, and multiple mutations are known. Some correlation is found between certain mutations and the phenotype. Three mutations account for 92% of cases in Ashkenazi Jews (Schuchman and Wasserstein 2016).

The pathological hallmark of the condition is the presence in the reticuloendothelial system of large vacuolated cells. Foam cells and ballooned ganglion cells are found in the CNS. Biochemically, there is a marked storage of sphingomyelin, a major component of normal myelin, in association with cholesterol in the spleen, liver and kidney. Storage is also present in the brain, although usually at a moderate level.

Clinical features of Niemann–Pick disease type B

Clinical features of Niemann–Pick disease type B (visceral type) is characterised by visceral involvement without neurological features and occurs mainly in older children and adults. An occasional patient may develop neurological signs.

In fact, the distinction between types A and B is not always clear-cut. Protracted neurovisceral forms with a course extending over periods of years are recognised and intermediate forms were the most common type in a large series, being observed in 12 of 25 patients (Pavlou-Pereira et al. 2005).

Treatment trials with enzyme replacement therapy (ERT) are in process.

Fabry Disease

Fabry disease is a rare, X-linked disorder is due to a deficiency of the A isoenzyme of alpha-galactosidase (ceramide trihexosidase) caused by several mutations of the GLA gene, mapping at Xq22. As a result, large amounts of trihexoside accumulate in various organs, especially the kidneys. Foam cells with vacuolated cytoplasm are found in smooth and striated muscle, in marrow and renal glomeruli. In the CNS, storage is confined to walls of the blood vessels and, to a lesser extent, to the autonomic nervous system. MRI may show peri-ventricular high signal and discrete lesions suggestive of demyelination.

Clinical manifestations usually begin in childhood in boys. Skin abnormalities may be the presenting feature, in the form of punctate angiectatic lesions (angiokeratoma corporis diffusum) that are commonly found on the genitalia or umbilicus or about the hips, but may rarely involve the face. Episodes of pain or dysaesthesiae in the limbs and sometimes in the abdomen are often the first symptoms. Pain is deep, of a burning character and occurs in episodes lasting from hours to weeks. These episodes are often associated with unexplained fever (Schiffmann and Ries 2016). Cornea verticillata is seen by slit lamp examination and is often present in heterozygotes (Watts and Gibbs 1986). Peripheral neurophyopathy involving small fibres has been reported and anhidrosis is frequent. Cochleovestibular and autonomic nervous system involvement is frequent. Approximately 30% of patients have cardiac defects including mitral valve prolapse and cardiomyopathy, and transient ischaemic episodes commonly occur (Ries et al. 2005).

The disease runs a progressive course, and CNS and visceral vascular accidents often occur with focal neurological signs, hypertension or myocardial infarcts. Renal involvement is the usual cause of death. Female carriers usually display late and milder symptoms.

Diagnosis is confirmed early by determination of alpha-galactosidase in plasma, leukocytes or fibroblasts in males. In females, genetic analysis is necessary.

Symptomatic treatment includes prevention of painful episodes, which can usually be achieved with carbamazepine, gabapentin or phenytoin, and therapy for renal insufficiency. Renal transplants have little effect on the CNS lesions, although sensory symptoms and renal function may improve.

Enzyme replacement therapy has changed the evolution of the disease. Large controlled studies in affected males have shown the safety and efficacy of recombinant enzyme preparations, which decrease pain and stabilise renal function (Clarke and Iwanochko 2005; Schaefer et al. 2005). Enzyme replacement therapy can be given under the form of agalsidase alfa (0.2mg/kg every 2 weeks) or agalsidase beta (1mg/kg every 2 weeks).

The quality of life of patients is significantly improved, especially the pain-related symptoms (El Dib et al. 2016). Preventive treatment for non-symptomatic female carriers is not generally advised. Antibodies against the enzyme have been found to develop (Linthorst et al. 2004) but their clinical significance is not yet clear.

Ceramidosis (Lipogranulomatosis, Farber Disease)

This rare disease is due to deficient activity of lysosomal ceramidase and is transmitted as an autosomal recessive character.
The onset is during the first weeks of life, with irritability, a hoarse cry and the appearance of nodular erythematous swellings around the wrists and other joints (Sands 2013). Severe motor and intellectual disability is frequent and convulsions are common. Cardiac valvular lesions may be present. Death occurs before 2–3 years of age although a mild form may allow survival for several years.

The basic lesion is a granuloma that forms around mesenchymal cells containing large amounts of ceramide. Neurons and glial cells are swollen by storage material.

Mucopolysaccharidoses (MPSs)

<table>
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<tr>
<th>Type</th>
<th>Eponym</th>
<th>Osseous visceral abnormalities</th>
<th>Neurological features</th>
<th>Urinary excretion of MPS</th>
<th>Mode of inheritance</th>
<th>Enzyme deficiency (gene location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IH</td>
<td>Hurler</td>
<td>Marked. Severe dwarfism</td>
<td>Severe</td>
<td>DS + HS</td>
<td>AR</td>
<td>alpha-L-iduronidase (4p16)</td>
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<tr>
<td>IS</td>
<td>Scheie</td>
<td>Mild¹</td>
<td>Mild</td>
<td>DS + HS</td>
<td>AR</td>
<td>alpha-L-iduronidase (4p16)</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>Marked. Severe dwarfism</td>
<td>Mild or moderate</td>
<td>HS</td>
<td>XR</td>
<td>Iduronosulfate-sulfatase (Xq28)</td>
</tr>
</tbody>
</table>
| III  | Sanfilippo | Mild. May be lacking at onset and seizures | Severe with progressive mental deterioration | HS | AR | A: Heparan-N-sulfamidase  
                                      B: alpha-N-glucosamine-N-acetylglucosaminidase  
                                      C: alpha-glucosamine-acetyl transferase  
                                      D: N-acetyl-alpha-glucosaminido-6-sulfatase (12q14) |
| IV   | Morquio (B milder) | Marked osseous anomalies | Absent (except as complication of bony lesions) | KS | AR | A: N-acetylgalactosamine-6-sulfatase (3p21–p14)  
                                      B: Beta-galactosidase (16q24) |
| VI   | Maroteaux–Lamy | Severe dwarfism and bony abnormalities | Absent (except as complication of meningeal involvement) | DS | AR | N-acetylgalactosamine-4-sulfatase (5p11–5q13) |
| VII  | Sly    | Mild to severe                | Absent to severe      | DS + HS                  | AR                  | Beta-glucuronidase (7q21–q22)   |

¹Limited to carpal tunnel syndrome; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; HA, Hyaluronidase; AR, autosomal recessive; XR, X-linked recessive.

Mucosulfatidosis (Multiple Sulphatase Deficiency, Austin Disease)

This is a rare disease characterised by absence of arylsulfatase A, B and C and of mucopolysaccharide sulphatase activity due to mutations in the formylglycine generating enzyme (Cosma et al. 2004; Lyon et al. 2006) and mutations in the SUMF1 gene. As a result, patients accumulate sulphatides, mucopolysaccharides and cholesterol sulphate in CNS and viscera and there is increased excretion of heparan sulphate in urine. Ichthyosis is a suggestive manifestation.

A recent review (Sabourdy et al. 2015) included 10 cases with mutations in SUMFG1 and showed that in the severe cases the symptoms of non-neurological as well as the psychomotor regression occur before 2 years of age.

Mucopolysaccharidoses (MPSs)

The mucopolysaccharidoses (MPSs) are a group of diseases caused by a deficiency of a lysosomal hydrolase that degrades glycosaminoglycans (GAGs).

Table 9.1 indicates the main characteristics, associating progressive accumulation of different GAGS within cells of different organs, resulting in somatic changes and neurological symptoms. Because of the involvement of different organs and tissues, a multidisciplinary follow-up is necessary after correct diagnosis, using GAGs in urine and then confirmation by biochemical assays in leukocytes and identification of the mutations. A full clinical evaluation is necessary including skeletal X-ray, echocardiography, eye examination, audiometry, MRI, electrocardiography etc.

Treatment options require early diagnosis. Haematopoietic stem cell transplantation in MPS I severe neurological type is an indication if the neurological condition is still good, preferably under the age of 2 years (de Ru et al. 2011).

For a number of MPS types, ERT has been developed, especially for those in the spectrum who have no severe neurological involvement. ERT is now currently used in MPS I and II attenuated cases, MPS IV and MPS VI. ERT has good results on the somatic involvement, but ERT does not pass the blood–brain barrier. Intrathecal therapies are also being developed for MPSII severe form, and in MPSIII (Sanfilippo). Other therapies such as substrate reduction or gene therapy are still under study.

Supportive therapy and careful follow-up remain necessary in all patients.
MPS IH (Hurler type)
The severe form, Hurler type, starts with symptoms within the first year of life. It is an autosomal recessive disorder (Fig. 9.2).

Clinical features of MPS IH
Characteristically within the first 6 months of life, frequent ear infections leading to hearing loss, umbilical and inguinal hernias can be alarm signs. Diarrhoea and failure to thrive occur often. After 6 months to 2 years, joints become stiff in elbows, wrists and knees. Hepatosplenomegaly, coarsening of the face, development of a lumbar kyphosis in the sitting position are the next signs together with a slowing in development. Corneal clouding develops and the head may become macrocephalic and somatic growth may slow down. MRI will show increased Virchow–Robin spaces and accumulation of storage material. Cardiac involvement, especially valve insufficiency and thickening, can occur early.

Diagnosis of MPS IH
The diagnosis is based on demonstration of an increase of urinary GAGs, mostly heparin sulphate and dermatan sulphate on electrophoresis, leucocyte analysis for L-iduronidase and mutation analysis. Some specific mutations can predict outcome (Kingma et al. 2013) which might be important in case of future neonatal screening for some of the MPS disorders.

Treatment of MPS IH
The general treatment is now haematopoietic stem cell transplantation. While awaiting a donor, ERT should be started and continued until full engraftment with transplantation.

MPS IH (Scheie type)
The milder forms of MPSI called Scheie disease have similar somatic features without neurological involvement, except the possibility to develop hydrocephalus (due to meningeal storage) and carpal tunnel entrapment. The diagnosis of the milder patients, is usually made later, around 3–4 years.

Treatment consists of lifelong ERT (laronidase Aldurazyme® 100U/kg) with good results on somatic features except skeletal abnormalities and cardiac involvement. Most patients develop antibodies against laronidase, which might influence treatment outcome.

MPS II (Hunter Disease)
The deficit lies in iduronate-2-sulphatase (Kato et al. 2005) which is an X-linked trait. The incidence is estimated as 1 in 80,000 to 1 in 130,000 male births. Depending on the presence or absence of neurological regression, a mild and a severe form can be recognised.
Clinical features of MPS II
In the severe form of the disease symptoms are similar to those in MPS I except presentation can be somewhat later. It starts also with a number of somatic features and then there is a cognitive decline, often with very difficult behaviour. As in MPS I, there is a spectrum with a more attenuated disease not affecting the brain in half of the patients. The neurological abnormalities in the attenuated type may include sensorineural deafness, retinitis pigmentosa, moderate hydrocephalus (Froissart et al. 2002) and carpal tunnel syndrome. For complete clinical presentations and treatments there are some excellent reviews, such as Scarpa et al. (2011).

Diagnosis of MPS II
An increase of GAGs (dermatan and heparan sulphate) is found in the urine of affected boys. Enzyme assay permits antenatal and postnatal diagnosis. The gene is located on Xq28 and a deletion is found in 30% of cases.

Treatment of MPS II
Haematopoietic stem cell transplantation is not a therapeutic option (Wraith 2008). ERT iduronate-2-sulphatase can be injected weekly at a dose 0.5mg/kg with good result on the somatic features especially when started early, but with no result on the intellectual decline (Rosella Tomanin et al. 2014). Intrathecal therapy is being studied and trials are ongoing.

MPS III (Sanfilippo Disease)
Sanfilippo disease is a genetically heterogeneous disorder of which four types resulting from four biochemical defects are known (Table 9.1).

Clinical features of MPS III
Infants can present with learning disabilities or with profound behavioural disturbance and sleeping problems (Wijburg et al. 2013). The clinical presentation is that of a progressive neurological and intellectual disability beginning between 2 and 6 years of age. Although corneal opacities are absent, abnormally coarse features and thick hair and eyebrows, present early and are superseded by the neurological disturbances. Epilepsy is frequent.

Diagnosis of MPS III
The diagnosis is often difficult initially because of the predominantly neurological and behavioural manifestations. Urine screening for GAGS should be done routinely in patients with unexplained regression. Increase of heparan sulphate but not dermatan sulphate is typically seen in MPS III. Enzyme assay and molecular analysis of the different genes permits differentiation of four types that are phenotypically indistinguishable. Antenatal diagnosis is feasible.

Treatment of MPS III
Attempts have been made with bone marrow and stem cell transplantation but seem to be not conclusive, resulting in further neurological deterioration. Intrathecal ERT and gene therapy are being now developed.

MPS IV (Morquio Disease)
Morquio disease has two types due to different genetic and enzymatic defects (Table 9.1).

Clinical features of MPS IV
The clinical manifestations are predominantly bone abnormalities and corneal opacities without intellectual disability. In type A, cognitive function is normal, but patients are severely affected by spondyloepiphyseal dysplasia, leading to extremely short stature, marked shortening and instability of the neck, deformity of chest and marked joint hyperlaxity. In the B form, symptoms are much milder.

Diagnosis of MPS IV
The diagnosis is usually clinical except in the milder types. Increase of urinary GAGs can be absent. The enzymatic analysis can be done for type A alpha-acetylglucosamine-6-sulphatase and in type B beta-galactosidase. Further molecular analysis is possible.

Treatment of MPS IV
Orthopaedic and neurological surveillance and treatment are essential. ERT has started with good tolerance and seeming improvement of the quality of life of the patients. Early treatment could probably further increase this positive effect.

MPS VI (Maroteaux-Lamy Disease)
Maroteaux-Lamy disease (MPS-VI) has diverse degrees of severity.

Clinical features of MPS VI
Short stature and visceral involvement are the main symptoms. Children may present in the first 2 years of life with frequent ENT infections and facial changes. Intellectual disability is absent (Vairo et al. 2015).

The main neurological complication is spinal compression, usually at cervical level, that may produce quadriplegia. This complication results from thickening of the meninges due to deposition of MPS and is difficult to treat surgically.

Diagnosis of MPS VI
In urine, there is an increase of GAGS mainly dermatan sulphate. Biochemical analysis of N-acetyl galactosamine-4 sulphatase on leukocytes and molecular confirmation of the gene mutation are diagnostic.
**TREATMENT OF MPS VI**

Enzyme replacement therapy Naglazyme (galsulfase) is now developed and given weekly with improvement seen in the 12 minute walk test (Brunelli et al. 2016).

**MPS VII (Sly Disease)**

Sly disease is a very rare disorder that may present with a wide range of phenotypic manifestations from nonimmune hydrops fetalis, through cases mimicking Hurler disease with severe neurodevelopmental delay, to cases with limited expression and without neurological features (Montaño et al. 2016). Recently an ERT has been developed and trials are starting.

**MUCOLIPIDOSES**

The mucolipidoses are rare disorders that have features of both the mucopolysaccharidoses and the lipidoses. Four types are described (Table 9.2; Fig. 9.3), although types 2 and 3 may be regarded as two degrees (severe and mild) of the same disease. They are transmitted as autosomal recessive characters.

**Sialidosis I**

*(Cherry-Red Spot Myoclonus Syndrome)*

Sialidosis I has a juvenile or adult onset and produces a rather pure intention and action myoclonus with a slow progression and no, or only mild, intellectual disability (Rapin et al. 1978; Young et al. 1987; Canagoglou et al. 2014). Minor dysmorphic features may appear at late stages. Also, it can present as a hydrops fetalis. Stalic acid is increased in urine.

The enzyme deficient is neuraminidase, which be measured only in fibroblasts. The gene is Neul.

**Oligosaccharidosis and Sialic Acid Disorders**

Oligosaccharidoses are a group of storage diseases with increased excretion of glycoproteins and decreased activity of lysosomal degradation of sugar side chains (Fig. 9.3).
These diseases are Salla disease, aspartylglucosaminuria, fucosidosis, alpha and beta mannosidosis, Schindler disease and sialidosis.

**Salla Disease**

Salla disease has two allelic disorders: Salla disease and infantile free sialic acid storage diseases resulting from mutations in the **SLC17A5** gene that codes for sialin, a lysosomal membrane protein that transports sialic acid out of the lysosomes.

Clinical manifestations include psychomotor delay of early onset during the first year of life, later followed by slowly progressive cerebellar and extrapyramidal dysfunction with severe intellectual deterioration. Involvement of the peripheral nervous system is evidenced by the decrease in nerve conduction velocity (Varho et al. 2000). There is a severe infantile type with early death in childhood, while the Finnish type Salla disease has a milder phenotype.

Both groups have intellectual disability; the infantile type has also severe visceral involvement, cardiomyopathy, and skeletal dysplasia (Kleta et al. 2004).

The disease is frequent in Finland but cases also occur in other populations (Robinson et al. 1997). Dysmorphic features appear only at a later stage. Diagnosis can be helped by finding vacuolated lymphocytes in blood and vacuolated cells in skin and conjunctival biopsy samples, and confirmed by demonstration of high levels of sialic acid in urine. Prenatal diagnosis is possible by determination of sialic acid in amniotic fluid. Several mutations are known (Myall et al. 2007).

**Aspartyl-Glucosaminuria**

This disease, almost only found in Finland, is due to a deficit of aspartyl glucosaminidase.

Clinical features are intellectual disability that begins in childhood or adolescence, lenticular opacities, bony changes as seen in MPS, and mitral valve insufficiency (Arvio et al. 1993). There is a striking dysmorphism with hypertelorism, short and broad nose, simple ears and thick lips (Arvio et al. 2004).

The diagnosis can be made by chromatography indicating increased excretion of glycosasparagines. Enzymatic measurement of aspartyl glucosaminidase can be done on leukocytes and the diagnosis confirmed by analysis the gene.

**Alpha-Mannosidosis**

Alpha mannosidosis is caused by several mutations in the gene for alpha-mannosidase (Beccari et al. 2003) resulting in neuronal storage of mannose-rich oligosaccharides (Fig. 9.3). A severe type (type I) has an infantile onset and is characterised by a Hurler-like appearance, intellectual disability, hearing loss, hepatosplenomegaly and dysostosis. There is often increasing macrocephaly, intellectual disability that remains stable and development of hearing loss. Recently ERT has been developed and studies are ongoing.

Type II has a juvenile onset and a milder course, but there is considerable overlap between the two forms. Cognitive deficit is variable and usually not progressive (Borgwardt et al. 2014).

**Beta-Mannosidosis**

Beta mannosidosis, due to deficiency of beta-mannosidase is much less frequent and variable with severe learning difficulties, behavioural problems, deafness and frequent infections.

**Fucosidosis**

Fucosidosis is caused by deficiency of the enzyme fucosidase which is responsible for storage of fucose in tissues. It is encoded by the **FUCA1** gene in which many mutations have been characterised (Lin et al. 2007).

Three types have been described: type 1 or severe type with early infantile onset, type 2 with onset around 18 months of age, and a rare type 3 with onset in adolescence. Type 2 is most common and has a slower course. Clinically, the condition presents with skeletal anomalies, cutaneous manifestations (angiokeratoma corporis diffusum involving
preferentially the genitalia and gingiva) and neurological symptoms often in the form of dystonia. There can be epilepsy and a mild dysostosis.

Diagnosis is made by the finding of abnormal oligosaccharides in urine, enzymatic analysis and molecular confirmation of the gene.

There is no treatment.

Galactosialidosis

Galactosialidosis results from a combined deficiency of neuraminidase and beta-galactosidase due to the absence of a protective protein that prevents proteolysis of the active enzyme. The disorder is genetically heterogeneous (Caciotti et al. 2013).

The onset of the juvenile form is between 5 and 10 years of age with cerebellar and extrapyramidal signs. Myoclonic seizures and action myoclonus usually develop after several years, and cognitive deterioration is late. There are no bony changes except for the frequent wedging of the first lumbar vertebrae. Coarse features progressively develop. An infantile form can closely resemble type 1 gangliosidosis (Galjaard et al. 1984).

CONGENITAL DISORDERS OF GLYCOSYLATION

There is a growing number of diseases due to defects in synthesis of the glycan moiety of glycoproteins or glycolipids and in attachment of glycan to proteins and lipids. Glycosylation of proteins is an essential step in co-translational maturation of polypeptides. This process is essential for viability and normal development. It concerns most extracellular proteins such as serum proteins (transferrin, alpha1-antitrypsin, alpha1-antichymotrypsin, some clotting factors,apolipoprotein C-III), most membrane proteins such as receptors, and intracellular proteins such as lysosomal enzymes (Fig. 9.4).

For the N-glycosylation of proteins, a glycan precursor is assembled from monosaccharide units on an anchoring isoprenoid alcohol, dolichol, in membrane of the endoplasmic reticulum. Each glycan precursor is then transferred to a specific asparagine residue in the peptide chain of a protein being synthesised by a ribosome and entering the endoplasmic reticulum. Transferrin is abundant in blood and is used as an indicator of the efficiency of the glycosylation system. Transferrin has two glycosylation sites. The protein is transported to the Golgi apparatus, and the glycans are modified in multiple steps (Jaeken 2003). Each fully modified glycan is terminated with two negatively charged sialic acid residues. Thus, the transferrin molecule carries a total of four sialic acid residues. If a genetic defect impairs synthesis of the precursor glycan in the endoplasmic reticum, one or both glycosylation sites of transferrin may remain unoccupied. Such defects are classified as congenital disorders of glycosylation type I (CDG-I).

In congenital disorders of glycosylation type II (CDG-II), the defect occurs in the modification of the already-transferred glycan. Isoelectric focusing (IEF) is used for investigating congenital disorders of glycosylation with the use of an agarose gel-based system, followed by immunoprecipitation in gel with an antibody to transferrin and staining of precipitate with Coomassie blue. Under conditions of normal glycosylation, most transferrin molecules carry four sialic acid residues (tetrasialo transferrin) and form a single major band on IEF. CDG-I defects are easily identified owing to the occurrence of transferrin isoforms with two or no sialic acid residues detected by means of IEF.

In CDG-II, the defect can result in transferrin molecules with no, one, two, three, or four sialic acid residues. A patient with a CDG-II defect has bands of approximately equal intensity at all positions from 0 through 3 or a smooth gradient of intensities, whereas in most cases, tetrasialotransferrin shows a more intense signal owing to residual activity.

Disorders due to defects in mannose-alpha-O-glycosylation are associated with Walker–Warburg syndrome and different forms of congenital muscular dystrophies such as muscle-eye-brain disease, Fukuyama congenital dystrophy and related myopathies.

Disorders of N-glycosylation result in multisystemic abnormalities that usually include the CNS. Some have no CNS involvement, and these will not be discussed here.

There is now a new classification for all CDGs (Jaeken et al. 2009): N-glycosylation, O-glycosylation, defects in glycosylated lipids, glycosphatidylinositol (GPI), anchor and glycosphingolipids (Freeze et al. 2015).

Examples are PMM2-CDG (CDG-Ia), PMI-CDG (CDG-Ib), ALG6-CDG (CDG-Ic), ALG3-CDG (CDG-Id), ALG12-CDG (CDG-Ig), ALG8-CDG (CDG-Ih), ALG2-CDG (CDG-II), DPAGT1-CDG (CDG-Ij), ALG1-CDG (CDG-Ik), ALG9-CDG (CDG-II), RFT1-CDG (CDG-In), ALG11-CDG (CDG-Ip), DDOST-CDG (CDG-Ir); TUSC3-CDG, MAGT1-CDG) with new ones added every year.

CDG type II involves malfunctioning trimming/processing of the protein-bound oligosaccharide chain. Examples are MGAT2-CDG (CDG-Ia), GCS1-CDG (CDG-Ib).

Diagnosis of CDGs is usually performed by isoelectric focusing of serum transferrin. The patterns are divided into two types.

Type 1 is characterised by elevated disialo- and asialotransferrin bands together with a decrease of tetrasialotransferrin.

Type 2 is characterised by increase of trisialo- and monosialotransferrin bands.

In addition to the isofocusing of transferrin, isofocusing of other serum sialylated proteins improves the diagnosis (Fang et al. 2004). Apolipoprotein C-III (ApoC-III) isoelectric focusing is used to screen for O-glycosylation defects either in isolation or in association with N-glycosylation defects. Three types of isoforms are recognised: ApoC-III, ApoC-III, and ApoC-III, depending on the number of sialic acid residues attached to the glycoprotein (Wopereis et al. 2007).
Figure 9.4 Schematic representations of the glycosylation process indicating the sites of defects in, respectively, CDG types I and II: (a) the elongation pathway in the endoplasmic reticulum; (b) the trimming pathway in the Golgi apparatus.
Examples of Type 1 CDG
PMM2-CDG (CDG-la)

Phosphomannomutase 2 (PMM2) deficiency (Fig. 9.5) is due to a defect in the second step of the mannose pathway (transforming mannose 6-phosphate into mannose 1-phosphate). Deficiency of GDP-mannose causes hypoglycosylation of numerous glycoproteins, including serum proteins, lysosomal enzymes, and membranous glycoproteins. PMM2-CDG is the most prevalent protein N-glycosylation disorder.

Clinical features
The clinical spectrum is very broad. The nervous system is affected in all patients and most other organs are involved in a variable way. The neurological picture starts with alternating internal strabismus and other abnormal eye movements. Congenital cataracts have been noted in a few cases. The majority of patients have some facial dysmorphism, inverted nipples, and peculiar body morphology with limb joint restrictions, thorax deformity and unusual fat pads above the buttocks over parts of the perineal region and/or on the fingers. In infancy there is poor feeding, failure to thrive and floppiness. Severe infections, hepatic failure, cardiac effusion with tamponade, and stupor occasionally associated with seizures and intracerebral haemorrhage can occur.

There is a nonprogressive intellectual disability. Most patients have an IQ around 50. Cerebellar ataxia and peripheral neuropathy, prevent independent ambulation in most cases. Recurrent episodes of dyskinetic or choreoathetotic movements may occur. Strabismus and retinitis pigmentosa regularly develop. Stroke-like episodes, related to cerebrovascular thrombosis, occur in half the patients after the age of 4–5 years with coma, seizures and transient blindness. About one-half of patients develop epilepsy.

During adolescence and adulthood the condition is static. Most patients achieve some social functioning but remain dependent.

Diagnosis
The diagnosis of PMM2-CDG is made by isoelectrofocusing (IEF) type 1 pattern and immunofixation of serum transferrin or by capillary zone electrophoresis of total serum. Other laboratory findings include increase of serum transaminases, hypoalbuminemia, hypocholesterolaemia, and tubular proteinuria.

The diagnosis is confirmed by a decreased activity of PMM2 in leukocytes or fibroblasts. Prenatal diagnosis is possible by enzymatic analysis of amniocytes or chorionic villus cells and mutation analysis of the PMM2 gene.

Several mutations have been identified in the PMM2 gene. The mutation leading to the R141H substitution is present in about 75% of the alleles of central European patients.

Brain MRI shows cerebellar and cerebral atrophy often from the neonatal period. However, this feature is not always present in newborn infants and in some patients cerebellar and cerebral atrophy can be progressive.

Figure 9.5 Carbohydrate-deficient glycoprotein syndrome type 1.
(a) Abnormal fat pads on the buttocks (b) Inverted nipples; note also feeding difficulties (tube feeding). (c) MRI, sagittal scan, showing marked cerebellar atrophy and relatively thin brainstem. (Courtesy Prof. Billette de Villemeur, Hôpital Trousseau, Paris.)
ALG6-CDG (CDG-Ic)

ALG6 encodes glucosyltransferase I. Its deficiency causes a defect in the attachment of the first glucose (of three) to the dolichol-linked Man9GlcNAc2 endoplasmic reticulum intermediate. This is the second most common protein N-glycosylation disease with at least 30 patients identified.

Clinical features are similar to those in PMM2-CDG but there is less dysmorphism and usually no retinitis pigmentosa or cerebellar hypoplasia.

Some glycoproteins have unusually low blood levels (particularly of factor XI, and coagulation inhibitors antithrombin and protein C). Analysis of the dolichol-linked oligosaccharides in fibroblasts shows an accumulation of the glycan intermediate Man9GlcNAc2.

ALG3-CDG (CDG-Io)

This is due to mannosyltransferase VI deficiency. Symptomatology includes severe psychomotor retardation, hypsarhythmia, postnatal microcephaly, optic atrophy, iris coloboma, hyperinsulinemic hypoglycaemia with islet cell hyperplasia, and brain and corpus callosum atrophy.

ALG12-CDG (CDG-Ie)

Due to mannosyltransferase VIII deficiency, the phenotypes show various combinations of facial dysmorphism, psychomotor retardation, hypotonia, inverted nipples, subcutaneous fat pads, skeletal dysplasia, and decreased serum IgG levels.

ALG8-CDG (CDG-Iii)

This CDG is due to glucosyltransferase II deficiency. Some show a severe disease with dysmorphism and multi-organ failure resulting in early death. One patient had a milder phenotype with hepatomegaly and protein-losing enteropathy. In another patient, there was prominent CNS involvement (macrocrania, psychomotor retardation, seizures, and diffuse leukoencephalopathy) besides entero-hepatic and renal disease.

ALG2-CDG (CDG-Ii)

The clinical picture in the reported patient with mannosyltransferase II deficiency was characterised by severe psychomotor retardation, infantile spasms, iris coloboma, cataract, and severe dysmyelination on brain MRI.

DPAGT1-CDG (CDG-Ij)

Deficiency of UDP-GlcNAc dolichol phosphate N-acetylgalactosamine 1-phosphotransferase is a defect in the very first step of dolichol-linked oligosaccharide biosynthesis. It was identified in a girl with severe psychomotor retardation, intractable infantile spasms, hypotonia, and microcephaly.

ALG1-CDG (CDG-Ik)

Reported patients with mannosyltransferase I deficiency showed intractable seizures, severe psychomotor retardation, and variable features such as dysmorphism, liver dysfunction, cardiomyopathy, nephrotic syndrome, hypogonadism, and depletion of b-cells.

RFT1-CDG (CDG-Ih)

This is a defect in the flippase that transfers Man5GlcNAc2-PP-Dol from the cytoplasmic to the lumenal side of the endoplasmic reticulum. Intrauterine growth retardation developmental delay, hypotonia with brisk tendon reflexes, drug-resistant epilepsy, deafness, and thrombotic complications (Ondruskova et al. 2012).

TUSC3-CDG

The defect is in one of the subunits of the oligosaccharyltransferase complex. It has been reported in several families with autosomal recessive, nonsyndromic intellectual disability and suggests a crucial role of this complex in cognitive functioning (Garbashi et al. 2011). IEF of serum transferrin shows a normal pattern.

MGAT2-CDG (CDG-IIa)

Deficiency in N-acetylgalactosaminyltransferase II was the first identified N-glycan processing defect. Besides neurological involvement (psychomotor retardation, drug-resistant epilepsy in three patients, behavioural disturbances), they presented with craniofacial dysmorphism, skeletal abnormalities, gastrointestinal disturbances, and growth retardation. IEF of serum transferrin showed a type 2 pattern.

MOGS-CDG (CDG-IIb)

This is a defect in glucosidase I, the first step in N-glycan processing. It was discovered in an infant with dysmorphism, hypotonia, and epilepsy. The urine showed an abnormal oligosaccharide identified as the tetrasaccharide (GLC (A1-2) GLC (A1-3) GLC (A1-3) Man). IEF of serum transferrin was normal.

Many other types have been published (Freeze et al 2015; Sparks and Krasnewich 2017).

PEROXISOMAL DISORDERS

PEROXISOMES

Peroxisomes are ubiquitous eukaryotic organelles that measure 0.1–1µm in diameter and are bound by a single membrane (Fig. 9.6). This membrane encloses the granular matrix that contains more than 70 different enzymes. Of the many metabolic pathways catalysed by the peroxisomal enzymes, the peroxisomal fatty acid beta-oxidation, alpha-oxidation, ether phospholipid (including the plasmalogens) synthesis, glyoxylate detoxification, H₂O₂ metabolism and pipecolic acid oxidation are the most relevant for human peroxisomal diseases or their diagnosis (Smith and Aitchison 2013; Braverman et al. 2016). Peroxisomes can be synthesised de novo from the endoplasmic reticulum.
Part IV  Metabolic and Heredodegenerative Disorders

[Problem Text]

Figure 9.6  Schematic representation of the main biochemical functions in peroxisomes.

DHAPAT, dihydroxyacetone phosphate acyltransferase; DHAP, dihydroxyacetone phosphate; Alkyl-G3P, alkyl-glycerol-3-phosphate; CoA, coenzyme A; VLCFA, very long chain fatty acids; THCA, trihydroxycholestanolic acid.

The main peroxisomal functions

Figure 9.6  Schematic representation of the main biochemical functions in peroxisomes.

DHAPAT, dihydroxyacetone phosphate acyltransferase; DHAP, dihydroxyacetone phosphate; Alkyl-G3P, alkyl-glycerol-3-phosphate; CoA, coenzyme A; VLCFA, very long chain fatty acids; THCA, trihydroxycholestanolic acid.

The main peroxisomal functions

**Peroxisomal Dysfunction**

The peroxisomal disorders can be divided into peroxisomal biogenesis disorders (PBD), where multiple peroxisomal functions are disturbed, and the single peroxisomal enzyme deficiencies. The PBD can be further divided into three subgroups: the Zellweger spectrum disorders (ZSD), selective PTS2-related PBD, and the disorders of peroxisomal fission. Except for X-linked adrenoleukodystrophy (X-ALD), all peroxisomal disorders have autosomal recessive inheritance.

**PEROXISOMAL BIOGENESIS DISORDERS**

**Zellweger Spectrum Disorders**

Zellweger Spectrum Disorders (ZSD) are caused by defects in one of the PEX genes, except for PEX7 where mutations cause rhizomelic chondrodysplasia punctata (RCDP) or adult Refsum disease, and PEX11beta, which is involved in a disorder of peroxisomal fission (Table 9.3).

The most severe of the ZSD is the classic Zellweger syndrome (Fig. 9.7). It presents in the neonate with profound hypotonia, poor sucking and swallowing with severe feeding problems, and depressed tendon reflexes. Epileptic seizures often start in the neonatal period and are typically therapy-resistant. Pigmented retinopathy and deafness are prevalent (Govaerts et al. 1985). Often cataracts develop. There is a recognisable dysmorphism, with a large anterior fontanelle, high forehead, abnormally round-shaped...
Table 9.3  Classification of human peroxisomal disorders

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Peroxisomes in liver</th>
<th>Peroxisomal enzyme defects</th>
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<tbody>
<tr>
<td>Zellweger syndrome</td>
<td>Absent</td>
<td>Generalized defects</td>
</tr>
<tr>
<td>Neonatal adrenoleukodystrophy</td>
<td>Scarce/Absent</td>
<td>Plasmalogens synthesis, phytanic oxidase, unprocessed thiolase</td>
</tr>
<tr>
<td>Infantile Refsum disease</td>
<td>Scarce/Absent</td>
<td>VLCFA oxidation, bile acid synthesis, plasmalogen synthesis</td>
</tr>
<tr>
<td>Rhizomelic chondrodysplasia punctata</td>
<td>Present and abnormal</td>
<td>Plasmalogens synthesis, phytanic oxidase, unprocessed thiolase</td>
</tr>
<tr>
<td>Zellweger-like syndrome</td>
<td>Present and normal</td>
<td>VLCFA oxidation, bile acid synthesis, plasmalogen synthesis</td>
</tr>
<tr>
<td>Fatty Acyl CoA Reductase-1 Deficiency</td>
<td>Present and normal</td>
<td>Severe intellectual disability, cataracts, growth retardation without rhizomelia (Buchert et al, 2014)</td>
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Group II: Single peroxisomal enzyme deficiencies involving beta-oxidation defects

<table>
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<tr>
<th>Disorders</th>
<th>Peroxisomes in liver</th>
<th>Peroxisomal enzyme defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked adrenoleukodystrophy</td>
<td>Present and normal</td>
<td>ALD protein</td>
</tr>
<tr>
<td>Pseudo-neonatal adrenoleukodystrophy</td>
<td>Present and abnormal</td>
<td>Acyl-CoA oxidase</td>
</tr>
<tr>
<td>Pseudo-Zellweger</td>
<td>Present and abnormal</td>
<td>Thiolase</td>
</tr>
<tr>
<td>Bifunctional enzyme deficiency</td>
<td>Present and normal</td>
<td>Bifunctional protein</td>
</tr>
</tbody>
</table>

Group III: Single peroxisomal enzyme deficiencies without beta-oxidation involvement

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Peroxisomes in liver</th>
<th>Peroxisomal enzyme defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refsum disease</td>
<td>Unknown</td>
<td>Phytanic acid oxidase</td>
</tr>
<tr>
<td>Pseudo-rhizomelic chondrodysplasia</td>
<td>Unknown</td>
<td>Plasmalogen synthesis</td>
</tr>
<tr>
<td>Di-(tri-)hydroxycholestanoic acidemia</td>
<td>Unknown</td>
<td>Bile acid synthesis</td>
</tr>
<tr>
<td>Mevalonic aciduria</td>
<td>Unknown</td>
<td>Cholesterol</td>
</tr>
</tbody>
</table>

VLCFA, very long chain fatty acid; ALD, adrenoleukodystrophy.

ears, flat eyebrow ridges, a broad and depressed nasal root and often single palmar creases. Redundant neck skin folds can be seen. The liver is enlarged and jaundice frequently develops. Patients show virtually no psychomotor development, and death typically occurs before the age of 1 year. Brain MRI shows polymicrogyria, which is typically perisylvian, and heterotopia. Germinolytic cysts are often seen. The ventricles are often mildly dilated. Myelination is delayed and white matter volume is decreased (Poll-Thé and Gärtner 2012). EEG shows a disturbed background and multifocal spikes. Abdominal ultrasound often shows cystic kidneys and hepatomegaly. Radiographs of knees and shoulders often show calcific stippling. Metabolite analysis shows abnormalities in different peroxisomal pathways.

The ZSD define a continuum from this classic Zellweger syndrome to a milder disease with focal neurosensory involvement and sometimes normal intelligence, without obvious dysmorphia, and characterised by prolonged survival past childhood and often into adulthood (Wanders 2004). Relatively milder mutations in the same genes that cause Zellweger syndrome are responsible for this spectrum. Neonatal adrenoleukodystrophy (ALD) and infantile Refsum disease, names that were given before the molecular cause of the disorders of the ZSD was known, belong to this
RCDP1 is characterised by rhizomelic shortening of the limbs, cataracts, intellectual disability and spasticity. Epilepsy can start at variable ages. Arthrogryposis occurs. Facial dysmorphism includes a broad nasal bridge, micrognathia, dysplastic ears and a highly-arched palate. Some patients have hepatomegaly and ichthyosis. Stippled epiphyseal calcifications present during infancy, and may disappear after the age of 2 years. A severe and a milder phenotype fitted well with the mild form of RCDP, but there was prominent demyelinating neuropathy, attributed to the higher levels of phytanic acid in RCDP5 compared with RCDP1 (Barry et al. 2015).

Disorders of Peroxisomal Fission

This is a group of disorders recently described in only a few patients. We can subdivide this group into a disorder where only peroxisomal fission is disturbed, PEX11beta deficiency, and disorders where both peroxisomal and mitochondrial fission are affected, caused by deficiency of dynamin-like protein 1, DLP1 (encoded by DNML1) or MFF. Deficiency of PEX11beta was described in one patient with congenital cataract, intellectual disability, childhood-onset progressive sensorineural hearing loss, axonal sensorimotor neuropathy, nystagmus and dry scaling skin. There were clinical deteriorations during intercurrent illness, which took a long time to recover, and the patient suffered migraine-like episodes accompanied by elevation of very long chain fatty acids (VLCFA). Peroxisomal parameters in blood and cultured fibroblasts were normal, except for the elevation of VLCFA after a migraine-like episode. Examination of peroxisome morphology in cultured fibroblasts showed excessive variation of peroxisomal size and decreased numbers of peroxisomes. Immunofluorescence for catalase showed cytosolic localisation of catalase in a small portion of the fibroblasts. This proportion increased to 90% after culturing the fibroblasts at 40°C. Sequencing of candidate genes involved in peroxisomal fission revealed nonsense mutations in PEX11beta.

Deficiency of DLP1 was first described in a single patient with combined mitochondrial and peroxisomal dysfunction. The patient presented in the first days of life with feeding difficulties, and profound hypotonia, paucity of voluntary movement, nystagmus, optic atrophy, areflexia and mild dysmorphic features. MRI showed abnormal anterior gyral development, systemic features, survival and biochemical markers improve. This also allows for more focal neurological signs to be noted and to develop, like ataxia, polyneuropathy, spasticity. Urolithiasis with oxalate stones also occurs in these patients. All patients within the ZSD are at risk for adrenal insufficiency and progressive inflammatory leukodystrophy comparable with X-ALD but the timing is unpredictable, as well as the factors that influence the onset.

Interestingly, at what is currently the mildest end of the spectrum, gene-specific disorders can be recognised. Mild mutations in PEX1 or PEX6 cause Heimler syndrome, characterised by enamel hypoplasia, nail abnormalities, variable retinal dystrophy and deafness, but normal intelligence (Rathb et al. 2015). This contrasts with findings in mild deficiency of PEX10, PEX2, and PEX12, where ataxia is the presenting sign. This raises questions about functions of the peroxins (PEX) genes outside general peroxisome biogenesis. Clinically, these patients in the mildest end of the ZSD illustrate the need to consider peroxisomal disorders in the diagnostic process of patients with isolated neurological deficits and normal intelligence. As the abnormalities in peroxisomal metabolites become less pronounced, inconstant and are sometimes completely absent with decreasing severity, diagnosis can be difficult, and in the future will depend on incorporation of peroxisomal genes in symptom-specific next generation gene panels; for example, ataxia gene panels.

PTS2-related PBD: Deficiency of PEX7 and PEX5L

Deficiency of PEX7 causes RCDP type 1 (RCDP1) and Refsum disease. Because of the deficiency of PEX7, ADHAPS and phytanoyl-CoA hydratase are not imported into the peroxisomal matrix. As a result, plasmalogens synthesis is impaired as well as phytic acid oxidation. RCDP1 is characterised by rhizomelic shortening of the limbs, cataracts, intellectual disability and spasticity. Epilepsy can start at variable ages. Arthrogryposis occurs. Facial dysmorphism includes a broad nasal bridge, micrognathia, dysplastic ears and a highly-arched palate. Some patients have hepatomegaly and ichthyosis. Stippled epiphyseal and extra-epiphyseal calcifications present during infancy, and may disappear after the age of 2 years. A severe and a mild form can be distinguished, both with moderate intellectual disability (IQ below 50) (Bams-Mengerink et al. 2013). In the severe phenotype, cerebral MRI displays delayed myelination, abnormalities in supratentorial white matter and progressive cerebral and cerebellar atrophy. In the mild phenotype, MRI is normal (Bams-Mengerink et al. 2006). The mildest form of PEX7 deficiency is a form of adult Refsum disease. As is clear from Table 9.3, the peroxisomal metabolites that are abnormal are phytic acid, which is elevated, and plasmalogens, which are decreased.

RCDP5, a novel PBD caused by mutations specifically affecting the long isoform of PEX5, was described. The phenotype fitted well with the mild form of RCDP, but there was prominent demyelinating neuropathy, attributed to the higher levels of phytic acid in RCDP5 compared with RCDP1 (Barry et al. 2015).

Spectrum, and correspond to intermediate and mild ZSD in the new classification (Braverman et al. 2016). Survival in intermediate ZSD is longer than in Zellweger syndrome, with death in the first decade. Patients with mild ZSD can reach adulthood. With decreasing severity, dysmorphism, initial development, systemic features, survival and biochemical markers improve. This also allows for more focal neurological signs to be noted and to develop, like ataxia, polyneuropathy, spasticity. Urolithiasis with oxalate stones also occurs in these patients. All patients within the ZSD are at risk for adrenal insufficiency and progressive inflammatory leukodystrophy comparable with X-ALD but the timing is unpredictable, as well as the factors that influence the onset.

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DISORDERS OF PEROXISOMAL ENZYME DEFICIENCIES

Deficiencies of the Peroxisomal b-Oxidation

As can be seen in Figure 9.6, the peroxisomes contain a complete set of enzymes for the beta-oxidation of VLCFAs and branched-chain fatty acids. The most important branched-chain fatty acids are pristanic acid, derived from phytanic acids, and the bile acid precursors. This means that if the defect includes branched-chain fatty acid beta-oxidation, bile acid synthesis is disturbed, and symptoms can include malabsorption and deficiencies of the fat soluble vitamins, with sometimes a coagulation disorder caused by vitamin K deficiency.

In X-ALD peroxisomal beta-oxidation is disturbed by defects in the adrenoleukodystrophy protein (ALDP), encoded by ABCD1. ALDP is necessary for the import of VLCP into the peroxisome. VLCP cannot be degraded and blood levels are elevated. Variable combinations of different phenotypes occur, the most devastating of which is the cerebral form of ALD. This form occurs in 35% of affected boys, and its occurrence currently cannot be predicted and can be discordant in the same family. Adrenal insufficiency and a later onset progressive neuromyelopathy are other presentations. In the context of peroxisomal disorders, it is noteworthy that a risk for inflammatory cerebral demyelination and adrenal insufficiency appears to occur in all disorders associated with elevated VLCP. This disorder is discussed in more detail in Chapter 10.

2-Methyl acyl-CoA racemase (AMACR) deficiency is a rare disorder with 10 reported patients, of which two were infants and eight adults. In infants, the disorder presents with cholestasis and fat soluble vitamin deficiency, while in adults the variable presentation is mainly neurological, with polyneuropathy, relapsing encephalopathy, epilepsy, thalamic lesions, tremor, cataact and retinopathy as possible symptoms (Haugarvoll et al. 2013).

Acyl-CoA Oxidase 1 (ACOX1) deficiency is characterised by impaired peroxisomal beta-oxidation of straight-chain VLCP. It is characterised by neonatal hypotonia, seizures, pigmentary retinopathy, hearing loss, hepaticomegaly, dysmorphic features and developmental delay. The clinical course is characterised by acquisition of few developmental milestones. Death is invariably before the age of 2 years. Imaging findings include delayed myelination, polymicrogyria, heterotopias, and inflammatory demyelination. Patients are at risk for adrenal insufficiency. However, milder forms with longer survival exist. Mild D-BP deficiency causes ataxia, sensorineural deafness, polyneuropathy, ovarian failure or azoospermia, retinopathy and mild intellectual disability with survival until adult age, which has also been called Perrault syndrome.

Deficiency of a-Oxidation: Adult Refsum Disease

Adult Refsum disease is caused by deficiency of phytanoyl-CoA hydratase (PHYH). The onset generally varies from adolescence to adulthood, and it is characterised by anosmia and early-onset retinitis pigmentosa as universal findings, with variable combinations of neuropathy, deafness, ataxia, and ichthyosis. Later in life, cardiac problems, including cardiomyopathy and arrhythmia can develop. Phytanic acid levels are elevated, usually above 200µmol/L.

As all phytanic acid enters the body through the diet, mainly by consumption of dairy products, levels of phytanic acid can be reduced by a diet restricted in phytanic acid. As human milk contains only little phytic acid, phytanic acid (and pristanic acid) is not a good peroxisomal marker in breastfed infants.

Deficiency of Ether-Phospholipid Synthesis

Three disorders have been described: RCDP2 (or DHAPAT deficiency), RCDP3 (or ADHAPS deficiency), and RCDP4 (or Fatty Acyl-CoA reductase 1 [FAR1] deficiency). Clinical symptoms and laboratory findings correspond to those described above for RCDP1, except that FAR1 deficiency is not associated with rhiomelia, and that phytanic acid levels are normal (Buchert et al 2014).

Deficiency of Glyoxylate Detoxification

Hyperoxaluria type 1 is characterised by increased excretion of oxalic acid in the urine, which leads without treatment to urolithiasis and nephrocalcinosis by crystallisation of calcium oxalate. As this leads to decreased renal function, levels of oxalic acid in the body increase, and complications of systemic oxalosis, including cardiomyopathy, polyneuropathy, bone disease, retinopathy, and calcium oxalate deposition in other organs follow (Wanders and Waterham 2006).

DIAGNOSIS OF PEROXISOMAL DISORDERS

Currently, clinical suspicion of a peroxisomal disorder will lead to analysis of one or more peroxisomal metabolites, generally some combination of VLCPs phytic acid, pristanic acid,
and plasmalogens. If one peroxisomal metabolite is abnormal, investigation of more peroxisomal metabolites from different peroxisomal pathways is performed. This allows to evaluate if the disorder is a PBD or a single peroxisomal enzyme defect. If only one pathway is affected, the enzyme activity can be measured in cultured skin fibroblasts or the gene can be sequenced directly. If metabolites from multiple pathways are deficient, analysis of peroxisomal pathways (beta-oxidation, alpha-oxidation, and plasmalogen synthesis) is done in cultured fibroblasts, together with visualisation of peroxisomal morphology and correct import of peroxisomal matrix proteins like catalase. Afterwards, the fibroblasts are complemented with different PEX genes to identify the responsible gene, which is then sequenced. When a strong-founded clinical suspicion of a peroxisomal disorder is not confirmed by analysis of peroxisomal metabolites in blood, it can be useful to proceed to fibroblast studies anyway, as patients are known who had no abnormal peroxisomal metabolites in blood, but whose fibroblasts showed re-localisation of catalase to the cytoplasm due to defective PTS1 import or morphologically abnormal peroxisomes. With the increasing use of next generation sequencing, a change can be expected towards earlier use of molecular genetics, possibly even directly following clinical suspicion in the near future. Another route to diagnosis will be the incorporation of peroxisomal genes in symptom-specific panels containing many non-peroxisomal genes, leading to a diagnosis even without clinical suspicion of a peroxisomal disorder. Enzymatic and biochemical studies in fibroblasts will then be reserved for confirmation of the pathogenicity of novel mutations.

TREATMENT OF PEROXISOMAL DISORDERS

Peroxisomal Biogenesis Disorders and Zellweger Spectrum Disorders

No proven aetiological therapies currently exist. Supportive measures need to be individualised depending on the severity of the disorder (Braverman et al. 2016). At the severe end of the spectrum, adequate feeding and seizure control seem most sensible. For patients at the mild end of the spectrum, logical choices would include rehabilitation with physical, occupational and speech therapy. Evaluation of auditory and visual function and remediation with hearing aids, cataract removal or correction of refractive errors can significantly improve quality of life in mildly affected patients (Witters et al. 2016). Yearly monitoring for adrenal insufficiency, with supplementation when necessary has been advised. Evaluation of malabsorption and supplementation of bile acids and fat soluble vitamins can be considered. Supplements of docosahexaenoic acid (DHA) can be useful if a deficiency exists, and a diet restricted in phytic acid can normalise blood phytic acid levels (Noguer and Martinez 2010). Evaluation of hyperoxaluria and treatment with increased fluid intake or urine alkalinisation becomes useful after the age of 4 years to prevent urolithiasis. It is important to recognise that these measures are futile in patients with Zellweger syndrome and that evidence for their usefulness in milder PBD is often merely anecdotal (Fig. 9.7).

PTS2 RELATED PEROXISOMAL BIOGENESIS Disorders

In PEX7-related Refsum disease, a diet restricted in phytic acid is advisable. In RCDP5, caused by mutations in PEXSL, phytic acid levels have been higher, accompanied by a demyelinating polyneuropathy, and a diet restricted in phytic acid is advisable (Barøy et al. 2015). Symptomatic therapy of complications is the mainstay of therapy in RCDP1.

Disorders of Peroxisomal Beta-Oxidation

'B-oxidation' X-linked Adrenoleukodystrophy

Lowering of VLCFA levels in blood with Lorenzo's Oil has no relevant benefit in established cerebral ALD, although discussion continues about the use in the presymptomatic phase. Haematopoietic stem cell transplantation (HCST) can stop progression of the cerebral form of X-ALD if performed early in the course of the disease. This is evaluated primarily with the Loes score on MRI. As a consequence of the X-linked nature of the disease, targeted familial screening often identifies asymptomatic family members. Current guidelines involve regular MRI to detect the first signs of demyelination, and subsequent bone marrow transplantation. From the age of 3 to 12 years, MRI should be done every 6 months, and afterwards yearly MRI is sufficient. As bone marrow transplantation is itself accompanied by significant morbidity and mortality, and 40–45% of patients never develop cerebral ALD and since bone marrow transplantation does not appear to prevent adrenomyeloneuropathy at adult age, systematic bone marrow transplantation of all presymptomatic male patients is not warranted (Engelen et al. 2012). Inflammatory signs are prominent and coincide with the presence of clinical symptoms, suggesting that they play a role in the mechanism of brain lesions.

General treatment includes screening for adrenal insufficiency every 6 months and supplementation if present. No specific treatment for adrenomyeloneuropathy exists.

ACOX1 deficiency

Aside from monitoring for adrenal insufficiency and general supportive and symptomatic therapy, treatment options are limited. One patient underwent hematopoietic stem cell transplantation HSCT without benefit.

D-Bifunctional Protein deficiency

In classic d-bifunctional protein deficiency (D-BP), monitoring for adrenal insufficiency and general supportive and symptomatic therapy are the only therapeutic options. In milder forms, measures as described above for treatment of malabsorption and DHA deficiency can be considered.
2-methyl acyl-CoA racemase (AMACR) deficiency
Therapy in children consists of measures for treatment of malabsorption and bile acid supplementation.

Refsum Disease: a-Oxidation
A diet restricted in phytanic acid is the mainstay of therapy. Weight loss should be avoided as this releases stored phytanic acid in the body. Acute decompensations can be treated by plasmapheresis. Symptomatic therapy with hydrating creams for ichthyosis and antiarrhythmic medication should not be overlooked.

Ether Phospholipid Synthesis (RCDP 2–4)
See RCDP1 above.

Glyoxylate Detoxification: Hyper Oxaluria Type 1
Increasing fluid intake and alkalinisation of the urine help lower levels of oxalic acid in the body and the urine.

DISORDERS OF AMINO ACID AND ORGANIC ACID METABOLISM

PHENYLKETONURIA AND HYPERPHENYLALANINAEAMIA
Phenylketonuria (PKU) and hyperphenylalaninaemia are due to a deficiency of phenylalanine hydroxylase (PAH) which converts phenylalanine to tyrosine in the liver. This enzyme requires tetrahydrobiopterin (BH4), which is formed from guanosine triphosphate (Fig. 9.8). The world-wide incidence of PKU is about 1 in 12 000.

Genetics
HPA is one of the most prevalent disorders of amino acid metabolism in the white population, occurring in approximately 1 in 10,000 live births. This autosomal recessively inherited disorder is caused by more than 500 mutations at the PAH locus. Different groups of mutations predominate in a given ethnic population, allowing prenatal diagnosis, carrier detection, and the prediction of the PKU phenotype linked with a particular haplotype. Some PAH mutations result in PAH deficiency with a residual enzymatic activity that is enhanced with BH4. In such cases, pharmacological dose of TBH results in, at least, a 30% decrease of blood phenylalanine levels.

Severe hyperphenylalaninaemia results in plasma phenylalanine values exceeding 1200 μM/L, in milder cases (HP) between 120–600 μM/L.

If untreated after a month this will lead to irreversible damage to the brain and severe intellectual disability. This is certainly necessary to keep PHe levels low within the first years of life.

Later high Phe levels can lead to concentration deficits and learning disability.

Pathogenesis
The clinical manifestations are thought to result from phenylalanine accumulation and its secondary effects on brain chemistry. The fact that PKU is most often accompanied by intellectual disability whilst HP is not, suggests that there is a threshold level of phenylalanine in extracellular fluids above which persistent postnatal (or fetal) HPA causes irreversible brain damage. If the threshold value is exceeded only later in life, after diet discontinuation in the early-treated PKU patients, reversible chemical changes appear that may affect neuropsychological function.

Abnormal myelination, reduction of brain weight and decreased myelin content are found in brain of untreated older PKU patients. These detrimental effects have been confirmed using the HPH-5 mouse model. Current and previous observations have led to the hypothesis that myelin reduction is due to inhibition of an oligodendroglial cell-specific ATP-sulfurylase that results in low content of sulfatides in myelin that in turn is exposed to proteolytic degradation. Consequently, neuronal loss and decreased interneuronal connections occur, as has been demonstrated by quantitative evaluation of neurotransmitter receptor density. If the results obtained in animals can be extrapolated to humans, special involvement of hippocampus and occipital area of the cortex could explain some of the neurophysiological disturbances observed in non- or poorly treated PKU patients. Abnormal brain protein synthesis due to polysome disaggregation and reduced rate of polypeptide chain elongation may result in low brain weight. Polysome disaggregation also occurs in heart and brain of fetal rats exposed to maternal HPA, a finding that has a bearing on the fetopathy associated with human maternal HPA.

Decreased DNA content and synthesis in neurons exposed to high levels of phenylalanine can also account for decreased proliferation of neurons, neuronal loss and impaired brain growth.

Clinical features
The clinical features of untreated PKU include intellectual disability, neurological abnormalities and extraneural symptoms (although the timing varies from patient to patient). Retarded intellectual development is often associated with microcephaly.
Abnormal EEGs are frequent (78–95% of cases), but only 25% of patients have seizures, most often of grand mal type. Psychotic behaviour with hyperactivity, destructiveness, self-injury, impulsiveness, and uncontrolled behaviour with episodes of excitement is not infrequent. The majority of patients present with lightly pigmented or eczematous skin. A peculiar musty odour has been repeatedly mentioned. The general physical development is usually good.

The clinical picture of PKU is now prevented by early diagnosis and treatment because of the implementation of neonatal screening. Phenylalanine (phe) levels are measured on dried blood spots collected during the first days of life. Deficiencies of co-factors need to be excluded early by investigation of pterins in blood or urine. Some patients with PKU or HP are BH4-responsive with a decrease of phe levels after oral administration of BH4.

Children with early diagnosis and adequate dietary and/or BH4 treatment will develop well and will have normal IQ’s.

**Treatment of PKU**

**Dietary treatment**

Recommendation on ideal levels of phe vary in different countries and change with age. The basis of diet is protein restriction, and adding amino acid mixtures without Phe (Bekhof et al. 2005; von Spronsen et al 2017).

**Tetrahydrobiopterin (BH4)**

In some patients BH4 or sapropterin (Kuvan) can reduce phe levels by more than 30% after a single dose of 10mg/kg; this is then considered as a BH4 responsive patient and daily doses of BH4 of 5–10mg/kg can continue, allowing a higher natural protein intake (Lindner et al. 2009; Thiele 2015).

**Maternal Phenylketonuria**

Mothers with PKU and high phe levels during pregnancy because of neglecting their strict diets can have infants who at birth have microcephaly, low birthweight, congenital cardiac defects and developmental delay. This is due to fetal damage caused by the high levels of phe. Phe probably competes with other neutral amino acids for placental and brain transport and may lead to tyrosine and tryptophan deficiencies leading to insufficient neurotransmitter concentrations. Recommended phe levels should be kept between 250–360µmol/L before and during the pregnancy.
**TYROSINAEMIA**

Five inherited disorders of tyrosine metabolism are known:

1. Tyrosinaemia type 1 (HT1) classic tyrosinaemia;
2. HT2 (Richner-Hanhart syndrome) with keratitis and blistering lesions on hands and feet;
3. HT3 might be asymptomatic or associated with intellectual disability;
4. Hawkininuria may be asymptomatic or associated with failure to thrive and metabolic acidosis in infancy;
5. Alkaptonuria leads to symptoms in adults with osteoarthritis and blue-coloured ears.

Tyrosinaemia type 1 (HT1) is the most frequent and will be discussed here.

**Tyrosinaemia Type 1**

Tyrosinaemia type 1 (HT1) is an autosomal recessive disorder caused by a deficiency of fumarylacetoacetase, the final enzyme in the catabolic pathway of tyrosine. Maleylacetoacetate and fumarylacetoacetate accumulate and are metabolised to succinylacetone. Succinylacetone inhibits δ-aminolaevulinate dehydratase (ALDH) activity and is responsible for abnormally high urinary excretion of δ-aminolaevulinic acid (δ-ALA) (Fig. 9.9).

**Clinical features of HT1**

There are three forms according to age at onset. An acute form starts before 6 months of age with liver failure. A subacute form manifests between 6 months and 1 year with liver failure, failure to thrive, coagulopathy, hepatosplenomegaly, rickets and hypotonia. A more chronic form presents after the first year with chronic liver disease, renal tubulopathy and end-stage renal failure, rickets, cardiomyopathy and/or porphyria-like syndrome. Hepatoma and end-stage renal failure are late complications.

Neurological crises, described as porphyria-like symptoms, may arise, during intercurrent infections, in patients affected with either the acute or subacute forms. Features include rapid progression of diffuse pain, mainly localised in legs and abdomen, associated with vomiting, irritability, hypotonia, painful episodes of opisthotonic posturing and brisk tendon reflexes. A rapidly ascending paralysis associated with areflexia may follow and results in respiratory insufficiency and death in the absence of assisted ventilation. Throughout this course patients remain conscious. Oral self-mutilation, such as tongue-biting, grinding and avulsion of the teeth, is observed especially during the initial phase.

**Diagnosis of HT1**

The diagnosis is made using neonatal screening and measuring of succinylacetone with tandem mass spectrometry; the diagnosis can be confirmed by the measurement of fumarylacetoacetase activity in lymphocytes or fibroblasts.

**Further mutation analysis of the FAH gene can be done. The gene is localised on chromosome 15q23-q25.**

**Treatment of HT1**

Since 1992, nitisinone, 2-(2-nitro-4trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC), treatment has been introduced. This drug blocks the tyrosine degradation and prevents the downstream toxic metabolites. This is now the standard of treatment at a dose of 2mg/kg/day during acute liver failure, reduced later to 1mg/kg/day maintenance (De Laet 2013). The treatment is associated with dietary restriction of Phe and tyrosine.

Liver transplantation is recommended for patients that do not respond to NTBC or when a hepatocellular carcinoma is suspected (increase of alpha-fetoproteins, AFP).

**DISORDERS OF BRANCHED-CHAIN AMINO ACID METABOLISM**

Maple syrup urine disease (MSUD), propionic aciduria, methylmalonic aciduria (MMA) and isovaleric aciduria (IVA) have similar presentations, mostly as early-onset severe neonatal forms with acute metabolic decompensation, an acute intermittent late onset with recurrent episodes of metabolic decompensation or as a chronic progressive form presenting as hypotonia, failure to thrive and developmental delay.

**Biochemical and Genetic Background**

These diseases result from defects of enzymes involved in the catabolism of leucine, valine and isoleucine (Fig. 9.10). These three neutral branched-chain amino acid (BCAAs) are initially
metabolised through a common pathway: a transamination that is followed by a thiamine-dependent decarboxylation, which is deficient in MSUD (step 1). The decarboxylation defect is responsible for accumulation of BCAAs and their corresponding keto-acids.

Leucine is further metabolised to acetoacetate and acetyl-CoA. Specific enzyme deficiencies may occur at every step. Isovaleryl-CoA dehydrogenase deficiency is responsible for isovaleric aciduria (step 2), isovalerate being a highly toxic substrate. Deficiency of 3-methylcrotonyl-CoA carboxylase, a biotin-dependent enzyme (step 3), produces 3-methylcrotonyl-glycinuria, as a result of either apo-enzyme decarboxylase mutation or abnormal biotin metabolism (see biotinidase responsive diseases).

3-Methylglutaconic aciduria type I (step 4) is another rare disease due to defective leucine catabolism (Ly et al. 2003). The catabolism of valine and isoleucine produces propionyl-CoA and methylmalonyl-CoA. Methionine and threonine, fatty acids with odd-numbers of carbons and the side-chain of cholesterol, are other precursors of propionyl-CoA. Propionyl-CoA forms methylmalonyl-CoA through a biotin-dependent decarboxylase (step 5) whose deficiency is due to an apoenzyme decarboxylase mutation (propionic aciduria) or to abnormal biotin metabolism. Methylmalonyl-CoA is converted to succinyl-CoA in two consecutive steps by the methyl-CoA epimerase (Dobson et al. 2006) and then by the B12-dependent methylmalonyl-CoA mutase (step 6). Deficient activity of each enzyme leads to methylmalonic aciduria. Abnormal B12 metabolism is responsible for variant forms of methylmalonic aciduria.

All but one of the disorders of this group are inherited in an autosomal recessive manner; 2-methyl-3-hydroxybutyryl CoA dehydrogenase deficiency is an X-linked disorder. Antenatal diagnosis can be performed through the measurement of metabolites in amniotic fluid, specific enzyme activity in chorionic villus samples or amniotic cells, and/or the determination of pathogenic mutations. Newborn infant screening programmes coupled with mutation studies have revealed that a number of patients with
either isovaleric aciduria or 3-methylcrotonylglycinuria detected by screening have mild or even asymptomatic phenotypes.

**Pathogenesis of Branch-Chain Amino Acid Disorders**
The pathogenesis of the cerebral involvement in BCAA disorders is poorly understood. In acutely ill patients, accumulation of toxic metabolites can be responsible for energy deprivation due to inhibition of certain enzymes involved in the pyruvate oxidation, in the Krebs cycle or in the mitochondrial respiratory chain. Susceptibility of basal ganglia to energy deprivation may explain their particular involvement in all these diseases, especially in methylmalonic and propionic acidurias. In MSUD patients, high leucine levels may result in defective catecholamine synthesis secondary to defective brain uptake of the neutral amino acids tyrosine and tryptophan. Similarly, interference of methylmalonic acid with succinate may reduce gamma-aminobutyric acid (GABA) synthesis. Irreversible changes may be the result of interaction with myelin synthesis due to defective transport of all the neutral amino acids (Schwab et al. 2006). In addition, accumulated propionyl-CoA and methylmalonyl-CoA are precursors of the synthesis of odd-numbered and methyl-branched long-chain fatty acids. Their incorporation into lipid layers may be responsible for abnormal lipid membrane synthesis in the CNS.

**Clinical Features of Branched-Chain Amino Acid Disorders**

**Severe Neonatal-Onset Form**
Development of a toxic encephalopathy with ketosis or ketoacidosis within a few days after an initial symptom-free period. The first signs are poor feeding, drowsiness followed by unexplained coma; followed by respiratory distress, hiccups, seizures, apnoeas, bradycardia and hypothermia. Generalised hypertonia and boxing or pedalling movements may occur.

Affected infants may have cerebral oedema with bulging fontanels, arousing suspicion of CNS infection. EEGs often show a burst-suppression pattern. Biochemical abnormalities include metabolic acidosis and ketonuria associated with hyperammonaemia and hyperlactacidemia. The overall short-term prognosis is improving, with early diagnosis and accurate management. Later, despite the treatment, acute life-threatening intercurrent episodes often occur, with clinical manifestations resembling those of late intermittent forms.

**Maple Syrup Urine Disease**
An intensely sweet maple sugar-like odour develops within a few days after birth. These patients do not develop dehydration or metabolic acidosis and routine biochemical analysis is normal. Abnormalities are found only in the plasma BCAAs, and in the urine organic acid analysis, 2-keto-acids are present.

![Figure 9.11 Methylmalonic aciduria. T2-weighted image showing symmetrical areas of high signal from the globus pallidus of an 8-month-old child. Delayed myelination is also evident.](DNPH screening test). The patients can rapidly deteriorate and become comatose.

**Isovaleric Aciduria, Propionic Aciduria and Methylmalonic Aciduria**

Dehydration is a frequent finding. Patients can also have metabolic acidosis with increased anion gap and ketonuria. Hyperammonaemia is a constant finding and lactate is moderately elevated. Because of the presence of neutropenia, thrombocytopenia or pancytopenia, there can be some confusion with sepsis.

**Intermittent and Late-Onset Forms**
In approximately one-third of patients, BCAA disorders present in childhood, or even in adolescence or adulthood. Recurrent episodes are frequent, while, in-between, these patients may seem entirely normal. The onset in most cases is precipitated by conditions that enhance protein catabolism (infection, trauma, etc.) or by excessive protein intake, but may equally occur without an overt cause. Recurrent coma or lethargy with ataxia are the main presentations. Most often, coma is not usually accompanied by other abnormal neurological signs. Ketoadidosis indicates a metabolic origin. Nevertheless, a few patients may present with acute hemiplegia and hemianopsia or signs and symptoms of cerebral oedema mimicking a cerebrovascular accident or a CNS tumour (Fig. 9.11).

Patients may die during such episodes. Severe cerebral oedema with brainstem compression has been reported in several MSUD patients. It appears to be a reversible cytotoxic oedema as judged from the results of diffusion-weighted imaging and magnetic resonance spectroscopy (MRS) studies.
This complication can be a major cause of death in all patients with BCAA presenting with acute decompensation. Some recover without sequel. Many children who survive severe, prolonged or recurrent metabolic disturbances are left with brain damage. Seizures are a common sequel. Neuroimaging usually shows cerebral atrophy and some delay in myelination. The most commonly affected areas are the brainstem, basal ganglia, and occipital periventricular and cerebellar white matter.

Patients with organic acidurias, and especially with methylmalonic or propionic acidurias can present with an acute or progressive extrapyramidal syndrome due to bilateral necrosis of the basal ganglia or extensive white matter degeneration.

**Chronic Progressive Forms**

Hypotonia, muscular weakness, nonspecific developmental delay and seizures are rarely the only revealing signs of isovaleric, methylmalonic or propionic acidurias. Most often they coexist with digestive and nutritional symptoms and failure to thrive.

**Other Diseases in This Pathway**

In 3-methylcrotonylglycinuria, patients identified through tandem mass spectrometry newborn screening are usually asymptomatic. 3-methylglutaconic aciduria type I may present with mild neurological impairment and speech delay (Nguyen et al. 2002). Malonic aciduria may present with isolated developmental delay or developmental delay associated with seizures, muscle weakness and cardiomyopathy (Salomons et al. 2007). 2-methylbutyrylglycinuria and isobutyrylglycinuria have been described in rare infants with muscle weakness and some developmental delay.

Isobutyryl-CoA dehydrogenase deficiency is a defect in valine metabolism and was first reported in a child with cardiomyopathy, anaemia, and secondary carnitine deficiency. Through newborn screening triggered by an elevation of C4-acylcarnitine in dried blood spots, more patients were found and some were completely asymptomatic. Isobutyryl-CoA dehydrogenase deficiency can be further confirmed by molecular genetic analysis of the gene encoding isobutyryl-CoA dehydrogenase (ACAD8).

2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency may be responsible for an X-linked progressive neurodegenerative disease with signs resembling the sequelae of a neonatal hypoxic–ischaemic brain injury from the second year of life (Poll-Thé et al. 2004). Movement disorders such as chorea associated with intellectual deterioration may result from progressive forms of many organic acidurias.

**Biochemical Diagnosis of Branched-Chain Amino Acid Disorders**

The diagnosis is based on the recognition of abnormal intermediate substrates and their by-products that result from the metabolic block. In MSUD patients, amino acid chromatography is characterised by high plasma and urine levels of leucine, valine and isoleucine and the presence of alloisoleucine. In contrast, all other enzymatic blocks result in plasma accumulation and urinary excretion of organic acids and are diagnosed using gas–liquid chromatography and mass spectrometry, while amino acid chromatography does not permit the diagnosis. Tandem mass spectrometry allows the recognition of these disorders through the abnormal acylcarnitine profiles that result from the accumulation of specific acylcarnitines, or measuring propionic aciduria or MMA and leucine, valine and isoleucine on the dried blood spot. The final diagnosis requires the measurement of specific enzymatic activities in fibroblasts or leukocytes, and/or the identification of pathogenic mutations in the genes concerned.

**Treatment**

Treatment is aimed at reducing toxic metabolites (Ogier de Baulny et al. 2005; Baumgartner et al. 2014). In the neonatal period, most acutely ill infants require aggressive nutritional therapy often associated with exogenous detoxification procedures. Long-term dietary treatment involves restriction in protein intake and in an otherwise well-balanced diet. Because some vitamins are cofactors of specific enzymatic steps, these vitamins must be systematically tested in each case. This therapeutic trial allows the recognition of vitamin-responsive patients who are less severely affected and may do well with a less strict diet. L-carnitine supplementation is systematically used in the treatment of organic acidurias. In isovaleric aciduria and 3-methylcrotonylglycinuria, L-glycine and L-carnitine supplementations increase metabolite urinary excretions and are effective means of detoxification (Sutton 2012).

Despite early diagnosis and treatment, at any age, these children are at risk for life-threatening metabolic imbalances and neurological sequelae. In addition, many patients with methylmalonic and propionic aciduria have progressive neurological dysfunction with intellectual impairment, ataxia, muscle weakness and poor nutritional states. Other complications may involve the kidneys, pancreas and heart. Facing these long-term complications, liver and kidney transplantations have been performed. However, none of these transplantations is able to prevent acute neurological degradation with basal ganglia necrosis (Leonard et al. 2001; Chakrapani et al. 2002).

Acute and chronic management should be supervised regularly and revised, based on regular updates (Chapman et al. 2012).

**Organic Acidurias**

**Glutaric Aciduria Type 1 (GA I)**

GA-I is an inborn error of lysine, hydroxylysine and tryptophan catabolism characterised clinically by an extrapyramidal
syndrome with dystonia and choreoathetosis, pathologically by striatal degeneration, and biochemically by a deficiency of glutaryl-CoA dehydrogenase (GDH) (Kölker et al. 2004; Hedlund et al. 2006; Kölker et al. 2007, 2011).

**Biochemical and Genetic Background**

GA-1 is an autosomal recessive disorder caused by a defect in GDH, a riboflavin-requiring enzyme that catalyses the dehydrogenation of glutaryl-CoA to glutaconyl-CoA and further to crotonyl-CoA (Fig. 9.12). The GDH gene is Figs. 9.12 and 9.13 on chromosome 19p13.2 and encodes a flavin adenine dinucleotide-dependent mitochondrial matrix protein that is involved in the catabolic pathway of L-lysine, L-hydroxylysine and L-tryptophan. More than 200 disease-causing mutations are known (Zschocke et al. 2000).

**Diagnosis**

Urinary acids analysis shows elevated glutaric acid, 3-hydroxyglutaric acid and glutaconic acid. Glutarylcarnitine can be detected by gas chromatography/mass spectrometry (organic acids) or tandem mass spectrometry (acylcarnitines). A definitive diagnosis comes from measuring the GDH activity in fibroblasts, leukocytes or liver biopsies, although correlation between residual activity and clinical phenotype is poor.

Prenatal diagnosis is available by determination of glutaryl-CoA dehydrogenase deficiency (solid bars).

**Pathophysiology**

The excitotoxic sequence initiated by glutaric and 3-hydroxy-glutaric acids (which exhibit structural similarities to the excitotoxic amino acid glutamate) is considered to play a major role in the pathophysiology of this disease. This process might involve the N-methly-D-aspartate (NMDA) receptors and cause apoptotic cell death. Furthermore, this conformational similarity may induce neurotransmitter imbalance in excitatory and inhibitory neurotransmission via inhibition of glutamate decarboxylase, the key enzyme in the biosynthesis of GABA (Kölker et al. 2004). Another possible pathogenic mechanism is that increased degradation of tryptophan via the kynurenine pathway may produce quinolinic acid during intercurrent inflammation. Quinolinic acid is neurotoxic and an agonist of the NMDA receptors.

The mechanism of age-specific destruction of specific cerebral structures has different hypotheses; most of the evidence points to impaired brain energy metabolism induced by accumulating glutaric acid, 3-OH glutaric acid and glutaric–CoA, which inhibits 2-oxoglutarate dehydrogenase. Glutaric acid impairs the dicarboxylic acid shuttle between astrocytes and neurons and 3-OH glutaric acid activates glutamatergic neurotransmission (Kölker et al. 2004).

**Clinical Features of GA 1**

Initially, affected children develop normally for several months, although they may have mild hypotonia, irritability and jitteriness. Macrocephaly is present at birth or is acquired in the first few months of life and can be an important early sign (Fig. 9.13). In typical untreated cases, an acute neurological deterioration resembling encephalitis precipitated by febrile illness, immunisation or surgical intervention (Kölker et al. 2007, 2011) occurs within 3 to 36 months, with lethargy, hypotonia, loss of head control, seizures, opisthotonus, grimacing, tongue-thrusting, rigidity and dystonia.

The characteristic neurological damage in these crises is acute bilateral striatal necrosis and, subsequently, a complex movement disorder while intellectual disability can be mild. Dystonia is the dominant extrapyramidal symptom, usually superimposed on axial hypotonia (Heringer et al. 2010). With age, there is a tendency for the development of a fixed dystonia and akinetic-rigid Parkinsonism.

Mobidity and mortality is high in patients who have had a crisis (Kölker et al. 2006). In 10–20% of patients, neurologic disease has been demonstrated in the absence of any documented encephalopathic crisis and has been termed insidious-onset (Busquets et al. 2000). Two patients with insidious-onset type were reported in whom striatal injuries had occurred before or shortly after birth, followed by latent periods of several months before disability was apparent. The risk for encephalopathic crises, however, declines after the age of 3 years. Appropriate treatment and especially emergency rules seem to improve the outcome, after positive neonatal screening (Kölker et al. 2011).

**Investigations in GA 1**

Cerebrospinal fluid (CSF) and neurophysiological investigations are normal. MRI studies performed in patients followed since birth show progressive CNS involvement. The radiological features characteristic of GA-1 seen in screened patients preceded the development of clinical disease. Widening of the sylvian fissure or lack of operculisation is the
most characteristic feature. More or less severe expansion of the pericerebral fluid spaces anterior to the temporal lobes is associated with hypoplasia of the temporal lobe. The mesencephalic cistern may be involved. Acute subdural hematomas or chronic subdural collections are classically reported, raising a suspicion of child abuse. Lesions of the putamen, either in isolation or in combination with the caudate nucleus, are commonly reported. Widespread involvement of the globus pallidus and thalamus, the dentate nucleus, the medial lemniscus and substantia nigra can be other radiological findings (Twomey et al. 2003).

These findings are in agreement with neuropathological reports showing that striatal changes are minimal in young affected patients but much more marked in older children, with neuronal loss and extensive fibrous gliosis. Degeneration of the globus pallidus and marked spongiosis of subcortical white matter have also been reported.

**Treatment in Glutaric Aciduria Type 1**

Metabolic treatment includes a low lysine diet, carnitine supplementation and intensified emergency treatment during acute episodes of intercurrent illness. However, the initiation of treatment after the onset of symptoms is generally not effective in preventing permanent damage. Secondary dystonia is often difficult to treat, and the efficacy of available drugs cannot be predicted precisely in individual patients.

Most patients remain asymptomatic if treatment is started in the newborn period. Dietary treatment in combination with carnitine and emergency treatment has been demonstrated to be effective in preventing neurological disease (Kölker et al. 2007). Recently the relative efficacy of each single component of this therapy has been evaluated, demonstrating that outcome was best in patients who received all three interventions (low lysine diet, carnitine, and emergency treatment).
and that deviations from basic metabolic treatment (low lysine diet, carnitine) resulted in an intermediate outcome. Disregard of emergency treatment recommendations was associated with a poor outcome (Heringer et al. 2010).

The use of a diet based on low lysine intake combined with lysine-free, tryptophan-reduced amino acid supplements to maintain adequate total protein intake has been associated with the most favorable neurological outcome and normal growth in some studies (Kölker et al. 2007; Heringer et al. 2010).

Treatment of intercurrent illness with high-calorie glucose infusions, rapid correction of fluid deficits and high-dose intravenous carnitine are important preventive measures. This regimen gives unsatisfactory results in symptomatic children, but could prevent further encephalopathic crises or progression of neurological deterioration. Conversely, treatment has considerably reduced the morbidity and mortality in presymptomatic patients, and nowadays this treatable disorder is considered in neonatal screening programmes. Neuropharmaceutical management of movement disorders is unsatisfactory. Effectiveness of baclofen or benzodiazepines to reduce involuntary movements may be limited by worsening the truncal hypotonia. Anticholinergic drugs, intrathecal baclofen, consecutive butulinum injections and pallidotomy are other therapeutic options that have been used in a very few or even single patients.

**Canavan Disease (N-Acetylaspartic Aciduria)**
This disorder, also known as spongy degeneration of the brain, presents clinically as a leukodystrophy. Urine or plasma analysis for N-acetyl aspartic acid (NAA) can now be considered as the biochemical marker of a disorder that was previously diagnosed by brain biopsy. It is caused by a deficiency of the activity of the aspartoacylase enzyme, which normally hydrolyses NAA to aspartate and acetate. Enzyme activity is present in various tissues (brain, leukocytes, liver, kidneys, adrenals, lungs and fibroblasts).

**Hydroxyglutaric Acidurias**
There are three diseases in this category: D-2-hydroxyglutaric aciduria (D-2-HGA), L-2 hydroxyglutaric aciduria (L-2-HGA) and combined D, L-2-hydroxyglutaric aciduria (D, L-2-HGA) (Kranadijk et al. 2012).

**L-2-HYDROXYGLUTARIC ACIDURIA (L-2-HGA)**
L-2-HGA is associated with a progressive neurodegenerative process with subcortical leukoencephalopathy, cerebellar atrophy and basal ganglia involvement. The disease is due to a defective flavine adenine nucleotide (FAD)-dependent L-2-hydroxyglutarate dehydrogenase with pathogenic mutations identified in its gene. The phenotype seems to be homozygous (Steenweg et al. 2009, 2010). The onset is insidious, starting in childhood with developmental delay, epilepsy and cerebellar ataxia. Most patients experience a very slowly progressive course. There can be progressive macrocephaly and extrapyramidal symptoms such as tremor and dystonia. Acute metabolic derangement does not occur. The patients can develop brain tumours. Several such cases have now been described suggesting L-2-HG may predispose to oncogenesis.

Steenweg et al. (2009) evaluated MRIs of 56 patients and found a highly characteristic pattern of MRI abnormalities in the subcortical cerebral white matter, the dentate nucleus, the globus pallidus, the putamen and the caudate nucleus. With progression of the disease, abnormalities of white matter and basal ganglia signal intensities become more diffuse, followed by white matter atrophy. The biochemical pattern is characterized by accumulation of L-2-HGA and lysine in body fluids, with usually higher concentrations in the CSF than in the plasma. Recessive mutations in \( L2HGDH \), summarised in Mutation Update, were reported (Steenweg et al. 2010).

**D-2-HYDROXYGLUTARIC ACIDURIA**
D-2-hydroxyglutaric aciduria (D-2-HGA), characterised by elevated levels of D-2-HG, is either autosomal recessive, resulting from mutations in \( D2HGDH \) (type I) or is caused by recurrent, usually de novo, dominant gain-of-function mutations in the \( IDH2 \) gene (type II).

Manifestations of both types of D-2-HGA include developmental delay, hypotonia, and seizures. Cardinal clinical manifestations common to the two genetic types include developmental delay, hypotonia and seizures. All type II patients were developmentally severely delayed more than the type I, and cardiomyopathy is only seen in type II. All other symptoms were present in the two types.

Presentation can be as a severe neonatal-onset form characterised by an early-onset epileptic encephalopathy with marked hypotonia, cortical blindness and serious developmental delay. A milder variant presents with more variable signs, most frequently hypotonia and developmental delay.

Cerebral MRI in severely affected patients shows delayed cerebral maturation, periventricular white matter abnormalities and the presence of subependymal cysts in the first months of life. In the mild phenotype, similar MRI alterations have been described. Biochemical diagnosis relies on strongly increased levels of D-2-HGA in plasma, urine and CSF that result from a defective D-2-hydroxy-glutaric dehydrogenase activity. Diagnosis is confirmed by gene sequencing and the identification of mutations in \( D2HGDH \) or mutations in \( IDH2 \) (Struys et al. 2005).

**COMBINED D-2-HYDROXYGLUTARIC ACIDURIA**
Combined D-2- and L-2-hydroxyglutaric aciduria (D, L-2-HGA) is characterised by elevated levels of both D-2-HG and L-2-HG acids in body fluids. Manifestation is as a severe neonatal epileptic encephalopathy, absence of developmental progress, respiratory insufficiency, developmental arrest and early death. Dysmorphism has been added to the clinical picture. The disease is due to recessive mutations in the gene \( SLC25A1 \) encoding a mitochondrial citrate carrier (Nota et al. 2013).
BIOTIN METABOLISM

Defects in biotin metabolism with multicarboxylase deficiency (MCD) result in severe neurological impairment with hyperlactataemia. Skin rashes, alopecia and breathing problems are the main manifestations. However, they are inconstant and the diagnosis should be considered in any case of hyperlactataemia (Baumgartner and Suormala 2016). Defective transport of biotin through the blood–brain barrier responsible for biotin-responsive basal ganglia disease (BRBGD) has been more recently described in patients from Middle-Eastern families (Ortigoza-Escobar et al. 2014). Because the condition is treatable with high doses of biotin, early diagnosis is important.

BIOCHEMICAL AND GENETIC BACKGROUND

Biotin acts as a cofactor in four carboxylases in humans: acetyl-CoA carboxylase, propionyl-CoA carboxylase, beta-methylcrotonyl-CoA carboxylase and pyruvate carboxylase. Isolated defects are known for the last three enzymes. Two defects in the intracellular utilisation of biotin are responsible for MCD: holocarboxylase synthetase (HCS) deficiency is a disorder of biotinylation of apocarboxylases; biotinidase deficiency is a disorder of biotin recycling. MCD leads to a characteristic organic aciduria comprising lactate, methylcrotonylglycine and propionyl-CoA derivatives. Enzyme defects are demonstrable in leukocytes or cultured fibroblasts, and biotinidase activity can be determined in serum.

Prenatal diagnosis of the two autosomal recessive disorders is feasible. The genes for biotinidase and HCS map to chromosomes 3p25 and 21q22.1 respectively (Aoki et al. 1995, Möslinger et al. 2003).

Thirdly, there is the biotinine-responsive basal ganglia disease (BRBGD) which has no biochemical markers. It is linked to mutations in an SLC19A3 transporter gene mapped to chromosome 2q36.3 (Zeng et al. 2005). A literature review (Ortigoza-Escobar et al. 2014) shows that most patients with BRBGD, the remaining patients onsets of disease between 1 month and 12 years; two-thirds of patients were classified as BRBGD, the remaining patients classified as having Leigh or Wernicke encephalopathies. This shows that BRBGD is a clinical continuum of this disease.

CLINICAL FEATURES OF MULTICARBOXYLASE DEFICIENCY

MultiCarboxylase deficiency (MCD) starts early with neurological symptoms, skin rashes and ketoacidosis, occurring usually in the neonatal period or later in infancy or childhood. In the neonatal period, patients can present with metabolic acidosis, hyperammonaemia, tachypnea, feeding problems, hypotonia and seizures. The diagnosis can be suspected by the abnormalities in the urinary organic acids.

High doses of biotin up to 200mg can give improvement but most respond at 10–20mg/day. Although there is an overlap in the age at onset, most neonatal forms are due to HCS deficiency, and the late-onset forms to biotinidase deficiency. The neonatal forms share clinical and biological features with neonatal-onset forms of other organic acidurias.

Biotinidase deficiency shows a less consistent picture: onset is insidious, with very variable neurological symptoms in the first year of life. In the severe cases (biotinidase activity below 10%), neurological and cutaneous symptoms occur between 2 and 5 months (Wolf 2010). Progressive lethargy with hypotonia and ataxia occurs following intercurrent infections. Refractory seizures and hypsarrhythmia are the most common manifestation and can remain isolated for long periods. Erythematous rashes, alopecia, conjunctivitis or blepharitis may be present at any time in the course, which is progressive even though transient recovery may occur. Chronic forms present with either a steady progression or a series of acute aggravations separated by periods of apparent normality. The most common neurological features are unsteady gait, episodes of ataxia, hypotonia and developmental regression. A few children presented with spastic paraparesis due to spinal cord demyelination.

The biochemical diagnosis is easy when lactic acidosis is associated with the specific organic aciduria. Measurement of biotinidase activity can be done on a dry blood spot and has been introduced in a number countries in the neonatal screening.

Mild intellectual disability, persistent ataxia, optic atrophy, abnormal visual evoked potentials, retinal impairment and sensorineural hearing loss may persist despite treatment (Weber et al. 2004).

Biotin-Responsive Basal Ganglia Disease

BRBGD is an autosomal recessive disorder starting in childhood with subacute episodes of encephalopathy, triggered by febrile illness and characterised by confusion, dysarthria, dystonia and quadriplegia. Biotin therapy during encephalopathic crises results in recovery within days.

Generalised convulsions have been associated in some patients during the initial period of the disease. Cerebral MRIs have revealed a uniform aspect with bilateral oedema and further necrosis of caudate heads and of the putamen.

The disease is associated with mutations in SLC19A3, the gene encoding for thiamine transporter hTHTR2 (Zeng et al. 2005). A literature review (Ortigoza-Escobar et al. 2014) shows that most patients with SLC19A3 mutations have an onset of disease between 1 month and 12 years; two-thirds of patients were classified as BRBGD, the remaining patients classified as having Leigh or Wernicke encephalopathies. This shows that BRBGD is a clinical continuum of this disease.

TREATMENT OF MULTICARBOXYLASE DEFICIENCY

Oral biotin reverses all the clinical and biological signs within a few days in patients affected with MCD. Biotin requirement is usually around 5–10mg/day. However, some
patients with severe HCS deficiency may require restriction of protein intake and higher doses of biotin (Baumgartner and Suormala 2016). Many symptomatic patients with biotinidase defects show some sequelae with mild cognitive delay, and hearing and visual impairment. Conversely, patients who have been treated preventively have normal development.

Early treatment with high doses of biotin (5–10mg/day) reverses all the neurological signs of BRBGD within a few days. They reappear within 1 month if biotin is discontinued. A systematic trial with biotin would be indicated in all patients who present with infantile bilateral striatal necrosis. In some patients, thiamine (10–40mg/kg/day) needs to be added (Ortigoza-Escobar et al. 2014).

**VITAMIN B12 DISORDERS**

The description of inherited disorders at each step of the vitamin B₁₂ (cobalamin) metabolic pathway has allowed new insights into the pathogenesis of both cobalamin and folate deficiencies. Deficiency of cobalamin or folate during pregnancy can cause severe malformation such as neural tube defects. After birth, deficiency of cobalamin and folate can cause anaemia, failure to thrive, recurrent infections, psychiatric and neurological symptoms. Clinical features are broadly similar for all inborn errors of cobalamin metabolism, with the exception of isolated adenosylcobalamin deficiency, expression of which is identical to that of methylmalonic aciduria (Whitehead 2006).

**BIOCHEMICAL BACKGROUND OF COBALAMIN DISORDERS**

The term cobalamin designates a group of compounds that function as coenzymes in two cellular reactions in humans: the generation of methionine from homocysteine with methylcobalamin as coenzyme and the conversion of methylmalonyl-CoA to succinyl-CoA using adenosylcobalamin as coenzyme. Dietary cobalamin, mostly obtained from animal proteins, is absorbed, bound to intrinsic factor, and then enters the bloodstream bound to transcobalamin-II to be taken up by cells via a specific surface receptor. Once within the cell, cobalamin undergoes a series of modifications resulting in methylcobalamin and adenosylcobalamin.

Depending on the site of the enzymatic defect, affected patients display methylmalonic aciduria or homocystinuria or a combination of both, as summarised in Figure 9.14. Blood levels of cobalamin are in the normal range. Different complementation groups A to J all now have known genes.

**GENETIC BACKGROUND OF COBALAMIN DISORDERS**

All defects of intracellular cobalamin metabolism are inherited in an autosomal recessive manner. Prenatal diagnosis can be performed by assaying amniotic fluid for amino acids and...
organic acids. Further confirmation can be obtained by either measuring appropriate enzymes in cultured chorionic villus samples or by molecular analysis where both mutations are known in a patient (Morel et al. 2005).

Pathophysiology of Cobalamin and Folate Deficiencies
Many neurological, haematological and biochemical features are common to acquired cobalamin and folate deficiencies, congenital defects in absorption or transport of cobalamin and folate, and intracellular defects in cobalamin and folate metabolism. All defects result in deficiency in methionine synthetase, which plays a central role in the pathogenesis of both cobalamin and folate metabolism disturbances (Hall 1990). Methionine synthetase deficiency has several putative secondary effects including the storage of folate as methyltetrahydrofolate (CH3THF) (folate trap putative secondary effects including the storage of folate as methyltetrahydrofolate (CH3THF) (folate trap theory), thus preventing their use in folate coenzyme synthesis; which appears essential for DNA synthesis and haematopoesis. Methionine synthetase deficiency also results in defective synthesis of methionine and of adenosylmethionine, which is the main methyl donor for methylation of many substrates such as neurotransmitters, myelin basic protein and phospholipids of plasma membranes. This defective methylation is thought to be the cause of subacute combined degeneration of the cord described in both acquired and congenital defects. Other factors may disturb the structure and function of the CNS in acquired and congenitally impaired cobalamin metabolism; for example, toxicity of accumulated homocysteine, which may be responsible for vascular injury and thromboembolism, and for the accumulation of methylmalonyl-CoA and propionyl-CoA due to defective mutase activity.

Clinical Features of Cobalamin Deficiencies

Congenital Vitamin B12 Deficiency
Cobalamin deficiency in breastfed infants of mothers who have subclinical pernicious anaemia or who are on a vegan diet without adequate B12 supplementation may result in neurological regression, abnormal movements and coma associated with megaloblastic anaemia. Vitamin B12 administration rapidly improves the neurological status, but further developmental progress may remain delayed (Gutierrez-Aguilar et al. 2005).

Cobalamin Absorption and Transport Deficiencies
Abnormal cobalamin absorption and transport may result from absent or abnormal intrinsic factor, defective ileal receptors or deficient transport into the cells.

Defects in cobalamin absorption and transport are responsible for a cobalamin deficiency syndrome characterised by a progressive disease with onset from 1 month to a few years of age. Usually the first symptoms are gastrointestinal, with failure to thrive, muscular weakness, drowsiness and megaloblastic anaemia. A few months later, peripheral neuropathy, myelopathy and encephalopathy develop, with marked developmental delay. Defects in absorption are due either to intrinsic factor deficiency or to defect in the cubilin–amnionless complex that acts as receptors for the IF-Cbl complex (Imerslund–Gräsbeck syndrome). Imerslund–Gräsbeck syndrome mutations are found in the ileal cobalamin receptor cubilin (CUBN) or its facilitator amnionless (AMN). Intrinsic factor deficiency mutations in the gastric intrinsic factor (Gifs) can be found.

Clinically, Imerslund–Gräsbeck syndrome and intrinsic factor deficiency overlap: starting with megaloblastic anaemia between 1 and 10 years, with anorexia, FTT and variable neurological symptoms such as neuropathy, cognitive problems, dementia; also recurrent infections due to neutrophil dysfunction. Patients with intrinsic factor deficiency can also present at a later age.

Defective transport which is essentially due to transcobalamin deficiency may, despite treatment, lead to severe neurological impairment (Trakadas et al. 2014). It can present very early in life and lead to early neurological symptoms if treatment is not started in time.

Defects in Intracellular Metabolism
Intracellular cobalamin deficiencies impairing the synthesis of methylcobalamin alone or of both methyl- and adenosylcobalamin present as three main types. The most frequent is a severe early-onset form described in newborn infants and young infants below 3 months of age. There is an increased homocysteine level and, in some, methylmalonic aciduria, low plasma methionine and S-adenosylmethionine.

CblF is a rare disorder (Rutch et al. 2009). The gene is LMBDRI, encoding for a lysosomal membrane protein, thought to act as a lysosomal exporter of cobalamin. Patients present early in life with poor feeding, failure to thrive, developmental delay, megaloblastic anaemia, pancytopenia and stomatitis.

CblC is the most frequent disorder of cobalamin metabolism (Carillo-Carascoet al. 2012). The disease starts, usually early, with progressive lethargy, hypotonia, abnormal movements, and/or seizures associated with pancytopenia and megaloblastic anaemia. Some patients also have multisystemic involvement including renal failure with haemolytic uraemic syndrome, cardiomyopathy and interstitial pneumonia. Retinal involvement with granular dyspigmentation of the macula and further peripheral pigmentary retinitis is an early sign in many CblC patients. Communicating hydrocephalus can be a further complication.

The early-onset form is related to specific mutations in the MMACHC gene, one of which (c271dupA) accounts for 40% of all disease alleles (Lerner-Ellis et al. 2009). A small number of patients present in childhood with progressive neurological deterioration, microcephaly, episodic seizures and megaloblastic anaemia, which usually leads on to the diagnosis. If untreated, acute neurological deterioration may occur with signs and symptoms resembling subacute degeneration of the cord. Rare affected adolescents and adults have presented...
similar subacute degeneration of the cord preceded by an acute deterioration of intellectual function and, sometimes, behavioural disturbances. In older patients, megaloblastic anaemia may be subtle, and borderline macrocytosis should be given particular attention (Fisher et al. 2014).

ClbD with mutations in the gene \textit{MMADHC} has three biochemical phenotypes with deficient synthesis of both cobalamin coenzymes causing combined methylmalonic aciduria and homocystinuria; deficiency of methylcobalamin synthesis causing isolated homocystinuria, or deficient adenosylcobalamin causing isolated methylmalonic aciduria.

Clinical symptoms are quite similar as in ClBc with the possibility of onset in infancy to adolescence (Miousse et al. 2009).

**Treatment of Cobalamin Deficiencies**

Responsiveness to vitamin B\textsubscript{12} supplementation must be systematically tested. Depending on the defect implicated, use of parenteral versus oral routes, pharmacological or high doses versus minute doses and hydroxycobalamin (1mg/day) versus natural cobalamin substrates (methyl-adenosylcobalamin) should be discussed. In both transport and intracellular defects, methionine replenishment with oral betaine or with extra methionine as well as folate could be essential. As predicted by the metabolic pathway of betaine, addition of folic acid can be helpful in long-term betaine therapy.

Because endogenous carnitine synthesis depends on methionine, carnitine supplementation can be useful in these conditions of methionine synthesis impairment. A normal-protein diet with avoidance of high protein intake is a logical support.

**DEFECTS IN FOLATE METABOLISM**

Folate is a methyl donor for homocysteine methylation to methionine. There are three independent types of membrane systems responsible for cross membrane transport of folate monoglutamate forms. These are the membrane folate receptor, the reduced folate carrier 1 (RFC1) and the proton-coupled folate transporter/heme carrier protein 1 (PCT/HCP1).

Several inherited disorders of folate metabolism and transport have been described Figure 9.15: MTHFR deficiency, MTR deficiency (caused by mutations in \textit{MTR} or \textit{MTRR} genes), cerebral folate deficiency (CFD) caused by \textit{FOLR1} mutations, hereditary folate malabsorption and glutamate formiminotransferase (FTCD) (Kirsch et al. 2013).

**Biochemical and Genetic Background**

Folates are derived from folic acid. Dietary folates are transported inside the intestinal cells by a specific carrier.
system, then transferred into the circulation, mainly in the form of CH$_3$THF. Circulating CH$_3$THF enters the tissues through a high-affinity carrier linked to intracellular methionine synthetase activity, which generates tetrahydrofolate (THF). Within the cell, a series of reactions (Kirsch et al. 2013) leads to the formation of the various folate coenzymes that constitute the donors or acceptors of single carbon units required for several metabolic processes. Defect in this specific folate transporter results in low levels of folates in serum and CSF and secondary deficiencies in folate-dependent reactions.

Purine and pyrimidine synthesis defects result in megaloblastic anaemia; deficiency in glutamate formimino transferase explains formiminoglutaric acid (FIGLU) excretion and defective methionine synthesis is responsible for combined homocystinuria and hypomethioninaemia. Glutamate formimino transferase and forimino-THF-cyclodeaminase activities are performed by a single protein, defects of which result in histidine catabolism deficiency with urinary excretion of FIGLU without involvement of crucial folate coenzymes that may be supplied by dietary sources.

CH$_3$THF reductase deficiency leads to defective synthesis of CH$_2$THF; the methyl donor for methionine synthesis from homocysteine, resulting in combined homocystinuria and hypomethioninaemia. Mutations responsible for the severe form of CH$_2$THF reductase deficiencies have been described in addition to polymorphisms that result in intermediate enzyme activity (Banka et al. 2011).

Cerebral folate deficiency is a clinically heterogeneous condition which leads to a severe decrease of CSF 5-methyltetrahydrofolate (5MTHF) in the presence of normal peripheral folate status. In 2009, Steinfeld et al. presented the first case associated with a mutation in the FOLR1 gene. Clinically patients present with stagnation or regression in development in the second year of life, with ataxia, autistic features and refractory myoclonic epilepsy. MRI of the brain commonly discloses hypomyelination and cerebral atrophy with, on spectroscopy, reduction of choline and inositol peaks (Pérez-Dueñas et al. 2010). Administration of oral folinic acid improved (1–5mg/kg/day) some patients but, in others, intravenous high doses of folinic acid (25mg/kg/day) were necessary (Delmelle et al. 2016).

**Clinical Features of Folate Defects**

**Methylenetetrahydrofolate (MTHF) reductase deficiency**

Patients present with many neurological signs and symptoms similar to those described in intracellular cobalamin defects involving methionine synthase. However, they do not have megaloblastic anaemia. In the neonatal-onset form, multi-organ involvement and retinopathy have not been described. Onset in childhood, with progressive neurological deterioration, is the most frequent course. A period of a few months’ normal development is followed by several months to several years of developmental slowing or arrest with poor head growth. Episodic seizures of various types are the rule. Hypotonia, ataxic gait and extrapyramidal movements are encountered in a few patients. In the absence of effective treatment, a third period of rapidly progressive deterioration follows with unexplained bouts of apathy, lethargy or coma often accompanied by central respiratory failure leading to death. Preceding or following these episodes the neurological signs worsen with further cognitive deterioration, gait disturbances, muscular weakness, spastic paresis and sometimes extrapyramidal symptoms with parkinsonian rigidity and tremors. In a few young patients, the second period is not observed, and they deteriorate abruptly following an acute event such as generalised tonic–clonic seizures. In adolescence and adulthood, many signs are similar to the late stage described above, except that most patients have normal development before the onset, the first sign being rapid cognitive deterioration and, in a very few patients, signs of schizophrenia. Less commonly, cerebrovascular complications may reveal the disorder. Biochemical investigations reveal mild homocystinuria and hypomethioninaemia in association with low to normal folate levels. Low CSF neurotransmitter levels have been reported (Burd et al. 2015). CT and MRI reveal non-specific cortical and subcortical atrophy and periventricular demyelination.

**Hereditary folate malabsorption**

Hereditary folate malabsorption is a clinical syndrome starting within the first few months of life. There is an impaired intestinal folate absorption and impaired folate transport into the CNS. After birth, affected infants develop severe folate deficiency with megaloblastic anaemia, diarrhoea, oral mucositis and recurrent infections. Poor feeding, failure to thrive, developmental delay and seizures can develop. The diagnosis is based on low levels of folate in serum, red blood cells and CSF, with undetectable amounts of CH$_3$THF. Mutations have been found in the SLC46A1 gene encoding for the PCFT which is present in the intestine and choroid plexus. Treatment with large doses of folinic acid can normalise folate levels. Supraphysiological folate concentrations are necessary to increase folate in CSF. However, methyltetrahydrofolate in red blood cells and in CSF can remain low. Supplementation with betaine or methionine may prevent neurological deterioration. Some patients remain intellectually disabled with variously combined neurological signs such as recurrent seizures, ataxia, athetosis and peripheral neuropathy.

**Glutamate formimino transferase deficiency**

The clinical expression of this disorder is variable (Whitehead 2006). In type I, intellectual disability, hypotonia, abnormal EEG and cortical atrophy are reported in half the cases, in association with folate-responsive megaloblastic anaemia. These
features appear between the ages of 2 weeks and 18 months. In type II, intellectual disability is mild with only a speech defect. There is no evidence of folate deficiency, and the biochemical hallmark is spontaneously high excretion of FIGLU. Mutations in the formiminotransferase cyclodeaminase (FTCD) gene have been identified in three children with the mild phenotype.

HOMOCYSTINURIAS

Inherited homocystinurias have, in common, accumulation of homocysteine with neurotoxicity; they encompass two distinctive clinical entities: classic homocystinuria due to cystathionine beta-synthase (CBS) deficiency and the rare inborn errors of cobalamin and folate metabolism. Classic homocystinuria is due to cystathionine beta-synthase deficiency. Clinically, the disease involves the eyes, bones, brain and vascular system. Intellectual disability can be present, but some patients have normal intelligence. Neurological signs include seizures, spasticity and psychiatric disorders.

Biochemical Background

In humans, methionine is catabolised to homocysteine through the transmethylation pathway (Fig. 9.16). Homocysteine is further degraded via the transulfuration route, yielding the end products sulphite and sulphate. Cystathionine beta-synthase catalyses the first step of this degradative pathway and requires vitamin B6 as a cofactor. Deficient activity of cystathionine beta-synthase is responsible for accumulation of homocysteine and methionine and decreased synthesis of cysteine (Schiff and Blom 2012).

About 50% of the homocysteine formed is remethylated to methionine. Enzymatic defects that affect remethylation are responsible for homocystinuria and hypomethioninaemia.

Genetic Background

Based on neonatal screening, the incidence of this autosomal recessive disease is about 1 in 335,000 live births. Three biochemically determined groups of patients are defined following B6 administration: one group is unresponsive, the second is clearly responsive, and the last has intermediate responsiveness.

The human cystathionine beta-synthase (CBS) gene maps to chromosome 21. More than 100 mutations have been characterised, some of them associated with B6-unresponsiveness. Cystathionine beta-synthase deficiency is expressed in cultured fibroblasts, lymphoblasts, cultured amniotic fluid cells and chorionic villus samples, allowing postnatal and prenatal diagnosis. In families where the mutations are known, direct analysis of the CBS gene allows rapid prenatal diagnosis.

Pathophysiology

While some data are available concerning homocystinuria, thrombosis and atherosclerosis, the relationship between the biochemical abnormalities and the development of intellectual disability, ectopia lentis or skeletal abnormalities remains obscure (Schiff and Blom 2012).

Clinical Features of Homocystinurias

Homocystinuria is a progressive multisystem disorder. The risk of developing manifestations of the disease increases with age.

B6-responsive patients are more mildly affected than B6-unresponsive ones. Four organ systems show major involvement: the eye, the bones, the CNS and the vascular system. Ectopia lentis is the most consistent finding. It is rarely present before the age of 2 years. Severe myopia should lead to further investigation. Fifty per cent of B6-unresponsive and responsive untreated patients have ectopia lentis by 6 and 10 years respectively. However, a normal ophthalmological examination at any age is no reason for rejecting the diagnosis. Optic atrophy, retinal degeneration or detachment, cataracts and corneal opacities appear to be secondary to lens dislocation. Individuals are often tall and slender with a marfanoid habitus and are prone to osteoporosis. Scoliosis and crush vertebral fractures can develop. Other frequently associated deformities include pectus carinatum, pes cavus, genu valgum, biconcave vertebrae and epimetaphyseal widening.

Intellectual disability is often the first recognised feature. Walking may be delayed and some patients have a ‘Charlie Chaplin-like’ gait. The IQ varies widely. B6-responsive patients have higher IQs (median 78) than B6-unresponsive ones (median 56).
Patients with homocystinuria have potentially life-threatening thromboembolic events. Vascular occlusions occur in any vessel at any age and may be the first manifestation. Cerebrovascular accidents may be responsible for optic atrophy, hemiparesis or seizures. Occlusions also occur in kidney, pulmonary artery, iliac vein, vena cava or coronary vessels. The risk of thromboembolic complications seems higher following intercurrent infections and surgery, and is responsible for a high mortality rate.

**Biological Findings in Homocystinurias**

Various abnormalities of clotting factors and platelets, and mildly low levels of folates and B₁₂ may be found. Usually, the cyanide–nitroprusside test (Brand reaction) in urine is positive, which is also positive in cystinuria and in the presence of sulphur-containing drugs. Definitive diagnosis is based on detection of sulphites in plasma and urine amino acid chromatography, which shows increase of homocysteine (50–200mmol/L); excess of sulphur-containing drugs. Definitive diagnosis is based on detection of sulphites in plasma and urine amino acid chromatography. In combined SO-XO deficiency (molybdenum cofactor deficiency), the previous pattern is associated with hypo-uricaemia and xanthinuria that inconstantly results in xanthine urolithiasis.

In both conditions, deficient sulphite oxidase activity, measured in skin fibroblasts, confirms the diagnosis. Prenatal diagnosis can be made by measuring sulphite oxidase activity or by DNA mutation analysis on chorionic villus samples (Johnson et al. 2002; Reiss and Johnson 2003).

For the molybdenum cofactor deficiency, mutations can be found in MOCS1, MOCS2 or GHPN – the three genes responsible for the synthesis of the molybdenum cofactor from GTP (Reiss and Hahnewald 2011).

**Pathogenesis of Sulfite Oxidase Deficiency**

Neuronal migration abnormalities on MRI suggest that the toxicity is initiated prenatally. However, the pathogenesis of the disease is only speculative. Accumulated sulphite may have direct CNS toxicity. Lack of sulphate may interfere with the synthesis of sulphate esters and of mucopolysaccharides. S-sulphocysteine may have neuroexcitatory properties and may be responsible for seizures (Fig. 9.17).

**Clinical Features of Sulfite Oxidase Deficiency**

Most patients present in the neonatal period with intractable seizures, feeding difficulties and severe developmental delay. The EEG may show a suppression–burst pattern. Further course is characterised by spastic quadriplegia, axial hypotonia and microcephaly. Seizures most often remain unchanged but spasms and choreoathetoid movements may appear. Peculiar facial dysmorphism is often noted. Ectopia lentis is mentioned during the clinical course in about 50% of cases. Most patients die within the first 2 years of life.

MRI studies show a rapidly progressive cystic leukoencephalomalacia that may suggest severe perinatal asphyxia (Dublin et al. 2002, Hobson et al. 2005). Pathologically there is severe cerebral atrophy, with ulegyria and multi-cystic subcortical lesions in the white matter. Severe neuronal loss, astrogliosis, microcavitations and spongiosis affect the whole cortex. A less severe form with prolonged survival and mild presentation has been described in a very few patients (Touati et al. 2000).

**Treatment of Sulfite Oxidase Deficiency**

Severe neonatal-onset forms are not amenable to any dietetic or pharmaceutical treatment. Some clinical improvement has been noted in two mildly affected patients treated with a low-cystine and low-methionine diet (Touati et al. 2000).
In molybdenum cofactor deficiency (with mutations in \textit{MoCD1}) a treatment with cyclic pyranopterin monophosphate (cPMP), a biosynthetic precursor of the cofactor, has led to better outcomes (Schwann et al. 2015).

### DISORDERS OF NEUROTRANSMITTER METABOLISM

#### BIOPTERIN AND CATECHOLAMINE METABOLISM

Recognition of inborn errors of monoamine metabolism relies mostly on the analysis of CSF and other body fluids for the detection of bioperins, catecholamines, serotonin, and their metabolites. Defects may be secondary to abnormal synthesis of tetrahydrobioperin (BH4), the cofactor for Phe, tyrosine and tryptophan hydroxylases, or affect the metabolic pathways of catecholamines and/or serotonin. They are responsible for dystonic syndromes, parkinsonism and progressive encephalopathies with abnormal movements (Table 9.4).

In neonates, these disorders may present with severe epileptic encephalopathy. Hyperphenylalaninaemia (HPA) is a leading sign in disorders where BH4 is defective in both liver and brain. Conversely, HPA is absent when the Tetra-HydorBioperin (THB) defect is expressed only in the brain, as well as in other defects of monoamine synthesis (Pearl et al. 2005). In addition, pyridoxal phosphate, the biologically active form of pyridoxine (vitamin B6), is a cofactor for aromatic L-amino acid decarboxylase. Thus, defects in pyridoxal phosphate are responsible for altered neurotransmission (Fig. 9.18).

We can distinguish disorders of:

1. Monoamine synthesis: (a) Without hyperphenylalaninaemia: including Segawa disease (autosomal dominant GTP cyclohydrolase 1 deficiency); tyrosine hydroxylase (TH)

<table>
<thead>
<tr>
<th>Table 9.4 Pterin patterns in tetrahydrobioperin deficiencies</th>
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<tr>
<td><strong>DHPR</strong></td>
</tr>
<tr>
<td>Neopterin (N)</td>
</tr>
<tr>
<td>Bioperin (B)</td>
</tr>
<tr>
<td>N/B ratio</td>
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<tr>
<td>% (B/B+N)</td>
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</tbody>
</table>

\textsuperscript{a}Presence of 7-bioperin characterizes this form.

\textsuperscript{b}Contrary to what would theoretically be expected, normal values are often found.

DHPR, dihydropteridine reductase; GTP-ch, guanosine triphosphate cyclo-hydrolase; PTPS, pyruvoyl-tetrahydropteridin synthetase; PCD, pteridine carbinolamine dehydratase.
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epinephrine and norepinephrine. It is an autosomal recessive disease on chromosome 11p15.5 resulting in cerebral catecholamine deficiency. Willemsen et al. (2010) showed that there are two phenotypes: an infantile-onset, progressive, hypokinetic-rigid syndrome with dystonia and a complex encephalopathy with neonatal onset.

The infantile-onset patients develop normally during the first months of life. Psychomotor development can be normal or only slightly delayed during the first 2 to 5 years of life. Thereafter, progressive motor signs appear. Affected individuals become hypokinetic and rigid, and dystonia develops. In the early stages, generally only one leg is involved, but with time both legs and also the arms, trunk, face and oropharyngeal musculature become affected. Initial complaints thus encompass abnormal posturing and walking difficulties, or frequent falls in those who already learned to walk before onset of symptoms. These children become wheelchair dependent within some years Table 9.5.

Severity of dystonia may fluctuate during the day (generally worse in the afternoon), but can also fluctuate within days, giving the impression of a paroxysmal dystonia especially in the early stages of the disease. Mild, nonprogressive intellectual disability can be found in patients with relatively early onset of motor symptoms, while cognitive functions appear unaffected in patients who develop symptoms after the first year of life. Besides the hypokinetic-rigid syndrome with dystonia, other features like tremor, chorea, oculogyric crises and ptosis, as well as behavioural or autonomic disturbances

SEGAWA DISEASE (GTP1 CYCLOHYDRAZINE 1 DEFICIENCY)

This was first described by Segawa in 1971. The hallmark of the disease was dystonia with diurnal fluctuation (see Chapter 19). The symptoms can start unilaterally or can present as an atypical spastic diplegia starting at school age or earlier. The enzyme is a rate–limiting step in synthesis of tetrahydrobioppterin, the cofactor for synthesis of catecholamines. The diagnosis can be suspected by low homovanillic acid, neopterin and 3-O-methyldopa in CSF. It is an autosomal dominant disease and the gene is located to 14q22.12-q22. The treatment, consisting of a low dose of L-dopa 3–7mg/kg/day, will immediately improve the symptoms.

TYROSINE HYDROXYLASE DEFICIENCY

Tyrosine hydroxylase catalyses the conversion of tyrosine into L-dopa. This leads to impaired synthesis of dopamine, epinephrine and norepinephrine. It is an autosomal recessive disease on chromosome 11p15.5 resulting in cerebral catecholamine deficiency. Willemsen et al. (2010) showed that there are two phenotypes: an infantile-onset, progressive, hypokinetic-rigid syndrome with dystonia and a complex encephalopathy with neonatal onset.

The infantile-onset patients develop normally during the first months of life. Psychomotor development can be normal or only slightly delayed during the first 2 to 5 years of life. Thereafter, progressive motor signs appear. Affected individuals become hypokinetic and rigid, and dystonia develops. In the early stages, generally only one leg is involved, but with time both legs and also the arms, trunk, face and oropharyngeal musculature become affected. Initial complaints thus encompass abnormal posturing and walking difficulties, or frequent falls in those who already learned to walk before onset of symptoms. These children become wheelchair dependent within some years Table 9.5.

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<table>
<thead>
<tr>
<th>Inborn error</th>
<th>Deficiency</th>
<th>Main neurological features</th>
<th>Diagnostic tests</th>
<th>References</th>
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<tr>
<td><strong>I—Disorders of monoamines</strong></td>
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<tr>
<td>'Malignant' hyperphenylalaninaemia</td>
<td>Disorders of tetrahydrobiopterin synthesis</td>
<td>Convulsions, intellectual disability, peripheral hypertonia, central hypotonia, dysautonomia</td>
<td>Abnormal urinary and CSF pteridine profiles. Increased phenylalanine. Decreased CSF HVA and 5-HIAA. DHPR* assay (dry blood spots)</td>
<td>Smith and Brenton (1995)</td>
</tr>
<tr>
<td>Hereditary dopa-responsive dystonia (Segawa disease, dominant)</td>
<td>GTP-cyclohydrolase</td>
<td>Dystonia with diurnal fluctuations</td>
<td>Decreased CSF HVA, 5-HIAA, biopterin and neopterin</td>
<td>Ichinose et al. (1994)</td>
</tr>
<tr>
<td>Hereditary dopa-responsive dystonia (Segawa disease, recessive)</td>
<td>Tyrosine hydroxylase</td>
<td>Dystonia with diurnal fluctuations</td>
<td>Responsiveness to small dose of L-dopa. Decreased CSF HVA, normal CSF 5-HIAA</td>
<td>Knappskog et al. (1995), Lüdecke et al. (1995)</td>
</tr>
<tr>
<td>Aromatic L-amino acid decarboxylase defects</td>
<td>L-amino acid decarboxylase</td>
<td>Central hypotonia, oculogyric crises, seizures, dystonia</td>
<td>Decreased CSF HVA and 5-HIAA</td>
<td>Korenke et al. (1997), Swoboda et al. (2003)</td>
</tr>
<tr>
<td>Dopamine beta-hydroxylase defect</td>
<td>Dopamine beta-hydroxylase</td>
<td>Bilateral prois, hypotonia, hypotension</td>
<td>Increased CSF L-dopa and HVA</td>
<td>Man int’ Veld et al. (1987)</td>
</tr>
<tr>
<td>Monoamine oxidase defect (X-linked)</td>
<td>Monoamine oxidase A</td>
<td>Behavioural disturbances, intellectual disability</td>
<td>Low urinary excretion of HVA and 5-HIAA</td>
<td>Abeling et al. (1994)</td>
</tr>
<tr>
<td><strong>III—GABA disorders</strong></td>
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<tr>
<td>4-Hydroxybutyric aciduria</td>
<td>Succinic semialdehyde dehydrogenase</td>
<td>Ataxia, hypotonia, speech retardation, intellectual disability</td>
<td>Increased 4-hydroxybutyrate and succinic semialdehyde (urine), increased CSF GABA. Enzyme assay (lymphocytes)</td>
<td>Jakobs et al. (1993)</td>
</tr>
<tr>
<td>GABA transaminase</td>
<td>GABA transaminase</td>
<td>Severe intellectual disability, hypotonia, excessive growth</td>
<td>High CSF and plasma GABA levels. Increased plasma growth hormone level. Enzyme assay (lymphocytes)</td>
<td>Jaeken et al. (1984)</td>
</tr>
<tr>
<td>Homocarnosinosis</td>
<td></td>
<td>Spastic paraplegia, intellectual disability, retinal pigmentation</td>
<td>High CSF homocarnosine</td>
<td>Pearl and Gibson (2004)</td>
</tr>
<tr>
<td>Hereditary hyperekplexia (Startle disease)</td>
<td>Glycine receptor alpha1 subunit mutation with high affinity for GABA</td>
<td>Exaggerated startle reflex, hypertonia, apnoea</td>
<td>Low free GABA levels in CSF</td>
<td>Berthier et al. (1995)</td>
</tr>
<tr>
<td>Dopamine transporter defect.</td>
<td>Early infantile progressive parkinsonism dystonia.</td>
<td>CSF: high HVA, reduced DAT levels.</td>
<td>gene SCL6A3.</td>
<td>(Kurian et al 2011)</td>
</tr>
<tr>
<td>Deficiency sepiapterin reductase</td>
<td>Axial hypotonia, language delay, oculogyric crisis, weakness, dystonia with diurnal fluctuation, psychiatric disturbances.</td>
<td>CSF: high biopterin and sepiapterin. levels.</td>
<td>Reduced enzyme activity. Sepiapterin in urine.</td>
<td>Koh et al. (2014)</td>
</tr>
</tbody>
</table>

DHPR, dihydropteridine reductase; CSF, cerebrospinal fluid; HVA, homovanillic acid; HIAA, hydroxyindoleacetic acid; GTP, guanosine triphosphate; GABA, gamma-Aminobutyric acid.
are absent or – if present – are found as a mild feature and in a minority of patients.

In almost all patients with this type, treatment with L-dopa results in an excellent response, sometimes even a miraculous improvement of the neurological condition. During follow-up, all patients continue to be asymptomatic or display only mild motor or cognitive impairment while on a low dose of L-dopa. They show no evidence of progressive disease, and tolerate L-dopa well during many years.

The second presentation according to Willemsen et al. (2010) is a complex encephalopathy with onset in the neonatal period or early infancy. Immediately after birth, or after a symptom-free interval of a few weeks, these patients rapidly develop a complex disorder. In most patients, the presenting signs are initially attributed to a complicated perinatal history, which makes estimation of age at onset difficult. The initial signs may differ between infants, but they all develop a varied neurological disorder that generally includes marked hypokinesia, bradykinesia and hypotonia, mixed with focal or generalised dystonic features and (often excessive) jerky movements like tremor and myoclonus, and that can also encompass bilateral ptosis and oculogyric crises. Diurnal fluctuation of symptoms may be present. However, especially in the most severely affected infants, dystonic crises occur within regular intervals of 4–5 days. Autonomic functions are often disturbed, especially during periods of dystonia or so-called lethargy-irritability crises, leading to excessive drooling, sweating, body temperature instability and marked periods of ‘pyrexia of unknown origin’. True epileptic seizures and non-epileptic paroxysms may further complicate the clinical picture. L-dopa treatment does not improve all signs equally, and it may take months before all effects of treatment become clear. Hypersensitivity to L-dopa is an important management problem in many of these patients, necessitating (extremely) low L-dopa doses at start, divided over four to six doses per day, and only increased over periods of weeks or months. Compared to the first type, prognosis with regard to final outcome is worse for motor as well as cognitive functions.

**Diagnosis and treatment**

CSF analyses will point to an impairment of dopamine synthesis with low levels of homovanillic acid (HVA) and methoxy-hydroxy-phenylglycol (MHPG), the end products of the dopamine pathway, contrasting with normal 5-HIAA and 3-O-methyl-dopa, the end products of serotonin and epinephrine pathways respectively. Serum prolactin is elevated due to dopamine deficiency. Phe tyrosine and pterin levels are all normal.

Treatment with L-dopa substitution is often poorly tolerated in the second group. Even low doses may result in side effects. However, with progressive increase from 2 to 6mg/kg/day over weeks or months, some improvement can be obtained. This can be combined with selegiline 5mg/kg day in a single dose (Dionisi-Vici et al. 2000).

**AROMATIC L-AMINOACID DECARBOXYLASE DEFICIENCY**

Aromatic L-Aminoacid Decarboxylase Deficiency (AADC) deficiency leads to a combined deficiency of catecholamines and serotonin as described in BH4 deficiency. Aromatic amino acid decarboxylase catalyses the decarboxylation of L-dopa and 5-hydroxytryptophan to dopamine and serotonin. The gene is located on 7p11.

Affected neonates can have feeding difficulties, autonomic dysfunction, hypothermia and hypotonia. However, they usually develop the characteristic signs at around 6 months with a progressive delay in motor acquisitions, oculogyric crises and a movement disorder with diurnal fluctuations. Serotonin deficiency leads to temperature instability, sleep disturbances, and irritability that can be linked to defective synthesis of melatonin from serotonin. Brun et al. (2010) reported 78 patients of whom most presented during infancy, but there were a few cases in adolescence with a milder phenotype.

CSF metabolites are characterised by reduced levels of HVA and 5-HIAA and increased levels of 3-O-methyl-dopa, high L-dopa and L-hydroxytryptophan. Pterin profiles, Phe and tyrosine are normal. The levels of histidine and taurine are also elevated. The finding of vanillactic acid on urinary organic acids analysis can suggest the diagnosis.

AADAC activity can be measured in plasma and the diagnosis can be confirmed by gene analysis. CSF concentration of pyridoxal phosphate can be low.

**Treatment** Effects of treatment are limited. The combination of cofactor supplementation vitamin B6, pyridoxal phosphate, MAO inhibitors, high-dose L-dopa and serotonergic agents can give some improvement. (Manegold et al. 2009) Table 9.6.

**SEPIAPTERIN REDUCTASE DEFICIENCY**

Sepiapterin reductase is the final step in the synthesis of BH4. The phenotypic spectrum of sepiapterin reductase deficiency (SRD) ranges from motor and cognitive deficits to sometimes minimal findings. Most affected individuals have nonspecific features in infancy including developmenta delay and axial hypotonia; other features develop over time. Clinical features in the majority include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises; symptoms show diurnal fluctuation and sleep benefit. Other common features include parkinsonian signs (tremor, bradykinesia, masked facies, rigidity), limb hypertension, hyperreflexia, intellectual disability, psychiatric and/or behavioural abnormalities, autonomic dysfunction, and sleep disturbances (hypersomnolence, difficulty initiating or maintaining sleep, and drowsiness). Friedman et al. (2012) reported a large series.

The diagnosis is made by CSF analysis and by analysis of the gene SPR.
### Table 9.6 Some vitamin disorders with neurological presentations

<table>
<thead>
<tr>
<th>Inborn errors</th>
<th>Enzyme deficiency</th>
<th>Possible neurological signs</th>
<th>Other features</th>
<th>Diagnostic tests</th>
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<td><strong>Biotin</strong></td>
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<tr>
<td>Multiple carboxylase</td>
<td>Holocarboxylase deficiency (neonatal onset).</td>
<td>Episodes of coma or progressive encephalopathy (Leigh), ataxia,</td>
<td>Skin rashes, alopecia, conjunctivitis</td>
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<td></td>
<td>biotinidase; holocarboxylase assay (leukocytes/fibroblasts)</td>
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<td>Defects in CNS transport</td>
<td>Biotin-responsive basal ganglia disease</td>
<td>Subacute encephalopathy, extrapyramidal and pyramidal signs,</td>
<td></td>
<td>Response to biotin</td>
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<tr>
<td></td>
<td></td>
<td>ganglia necrosis</td>
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<td><strong>Vitamin B12</strong></td>
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<tr>
<td>Absorption defects</td>
<td>Intrinsic factor deficiency</td>
<td>Developmental delay, subacute combined degeneration</td>
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<td>Congenital Biermer disease</td>
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<td>skin rashes, mucositis, proteinuria</td>
<td>test; intrinsic factor Transcobalamin II assay</td>
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<tr>
<td>Immersslund–Gräsbeck syndrome</td>
<td>Cubilin–amnionless complex deficiency</td>
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<td>Transport defect</td>
<td>Transcobalamin II deficiency</td>
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<td><strong>Intracellular metabolism</strong></td>
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<tr>
<td>CblA, CblB</td>
<td>Adenosyl synthesis defect</td>
<td>cf. Methylmalonic aciduria Developmental delay, seizures, microcephaly, retinopathy, dementia (in older patients)</td>
<td>Anaemia (macrocytic), multivisceral failure (early onset)</td>
<td>Methylmalonic aciduria Methylmalonic aciduria + homocystinuria + hypomethioninaemia</td>
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<tr>
<td>CblC, CblD, CblF</td>
<td>Adenosyl- + methylcobalamin synthesis defect</td>
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<tr>
<td>CblD 1/2</td>
<td>Methylcobalamin defect or adenosyl synthesis defect</td>
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<td>Homocystinuria + hypomethioninaemia or methylmalonic aciduria</td>
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<td><strong>Folate</strong></td>
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<tr>
<td>Malabsorption</td>
<td>PCFT/HCP1 gene</td>
<td>Intellectual disability, seizures, ataxia, athetosis, peripheral neuropathy, brain calcifications</td>
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</tr>
<tr>
<td>Homocystinuria ‘variants’</td>
<td>Methylene tetrahydrofolate</td>
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<tr>
<td><strong>Vitamin B6</strong></td>
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<tr>
<td>Pyridoxine dependency</td>
<td>Antiquitin</td>
<td>Seizures (onset neonatal to 1 year)</td>
<td>Therapeutic response to pyridoxine (50–100 mg i.v. during EEG monitoring); alpha-amino-adipic semialdehyde (plasma, urine, CSF)</td>
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<tr>
<td>Pyridoxine 5′-phosphate oxidase</td>
<td>PNPO gene</td>
<td>Seizures (onset neonatal)</td>
<td>Low birthweight</td>
<td>Resistance to pyridoxine, therapeutic response to pyridoxal phosphate</td>
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<td><strong>Vitamin E (Koenig 2003)</strong></td>
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<tr>
<td>Selective malabsorption (specific)</td>
<td>Alpha-tocopherol transporter retinitis pigmentosa</td>
<td>Peripheral neuropathy,</td>
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<tr>
<td>Secondary deficiency</td>
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<td>Peripheral neuropathy, retinal degeneration</td>
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<td>Low liposoluble vitamins, low cholesterol + triglyceride</td>
</tr>
<tr>
<td><strong>Hartnup disease</strong></td>
<td>Neutral amino acids transporter</td>
<td>Ataxia, psychosis, lethargy; usually asymptomatic</td>
<td>Pellagra-like rash</td>
<td>Neutral aminoaciduria; response to nicotinamide therapy (50 mg/day)</td>
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<td>(Kraut and Sachs 2005)</td>
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</table>

*Continued*
Inborn errors | Enzyme deficiency | Possible neurological signs | Other features | Diagnostic tests
---|---|---|---|---
Cerebral folate deficiency | MRI: hypomyelisation or leukoencephalopathy | Decreased folate receptor alfa in choroid plexus | Low CSF folate levels, with normal plasma levels | FOLR1 gene. Response to folinic acid (10 mg/d)
Thiamine transporter 1 | Diabetes mellitus, neurosensory deafness | Neurosensorial deafness | Megablastic erythropoiesis | Gene SLKC19A2
Thiamine transporter 2 | Dystonia, speech difficulties, confusion | MRI: caudate and putamen symmetrical lesions | Gene SLC19A3 | Response to biotin plus thiamine
Brown-Vialetto-van Laere | Progressive ponto bulbar paralysis, deafness, nystagmus, optic atrophy, sensory ataxia | Axonal neuropathy and progressive respiratory failure | Low plasma flavin concentrations and pattern blood of acylcarnitines suggesting MAD deficiency | Gene SLC52A2 and SLC52A3. Response to rivoflavin at different doses

CNS, central nervous system; Cbl, cobalamin; PCFT, proton-coupled folate transporter; HCP, heme carrier protein; PNPO pyridox(am)ine 5'-phosphate oxidase; MAD, multiple acyl-CoA dehydrogenase.

**Treatment**

L-dopa in combination with carbidopa is the main therapy used to correct CNS dopamine deficiency; 5-hydroxytryptophan (5-HTP), also in combination with carbidopa, has shown additional clinical benefit in some. When L-dopa/5-HTP/carbidopa are not tolerated or sufficiently effective, some individuals may benefit from use of other agents such as monoamine oxidase inhibitors, serotonin reuptake inhibitors, melatonin, dopamine agonists, anticholinergics, and methylphenidate.

**DOPAMINE B-HYDROXYLASE DEFICIENCY**

Dopamine B-hydroxylase deficiency is characterised by disturbed noradrenergic function but normal parasympathetic cholinergic function. Clinically, patients present with orthostatic hypotension. The combination of ptosis of the eyelids in children together with hypotension is suggestive. The diagnosis is made by the absence in plasma of norepinephrine and epinephrine and increase of plasma dopamine as well as the anamysis for mutations in the gene for this disorder.

L-dihydroxyphenylserine (L-Dops) can improve orthostatic hypotension (Man in’t Veld et al. 1987).

**MONOAMINE SYNTHESIS WITH HYPERPHENYLALANINAEMIA**

This is due to pyruvoyl-tetrahydropterin synthase (PTPS) deficiency and dihydropteridine (DHPR) deficiency. These children present with a positive neonatal screening for phenylalaninaemia, but despite a controlled diet develop signs of neurotransmitter deficiencies such as hyper and hypotonia, oculogyric crises, dystonia and diurnal fluctuation. Treatment is such as described for the cases above.

**MONOAMINE OXIDASE DEFICIENCIES**

Monoamine oxidase A and B catalyse the deamination of serotonin, epinephrine and norepinephrine. Both the genes are located on the X chromosome. Point mutations and large deletions including MAO-A and B have been described in boys with a severe intellectual disability (Guo et al. 2008).

**INBORN ERRORS OF GAMMA-AMINOBUTYRIC ACID METABOLISM**

GABA (4-aminobutyric acid), a major inhibitory neurotransmitter amino acid, is synthesised from glutamic acid via glutamate decarboxylase. The catabolic steps comprise transamination, which yields succinate semialdehyde, and oxidation to succinate, which finally enters the Krebs cycle. Pyridoxal phosphate is a coenzyme for all these three reactions. A secondary route, catalysed by a dehydrogenase, converts succinate semialdehyde to gamma-hydroxybutyrate, which is further oxidised (see Fig. 9.18). In addition, the major precursor of glutamate in neurons is glutamine, which is synthesised in glial cells via glutamine synthetase. Glutamine is then transported to neurons, where glutamate and then GABA are metabolised. This GABA shuttle between neurons and glial cells allows the maintenance of this system. Homocarnosine is the dipeptide form of GABA. The most frequent defect in
GABA metabolism is succinic semialdehyde dehydrogenase. GABA transaminase deficiency and homocarnosinosis are very rare disorders (Fig. 9.19) (Pearl et al. 2015). Defective glutamine synthesis is a newly described disorder in neonates with severe brain malformation.

**4-HYDROXYBUTYRIC ACIDURIA**

4-hydroxybutyric aciduria is inherited in an autosomal recessive manner, and is characterised by the accumulation of gamma-hydroxybutyric acid (GHB) and GABA in body fluids secondary to succinic semialdehyde dehydrogenase (SSADH) deficiency. Deficient SSADH activity has been demonstrated in lymphocytes and fibroblasts. The gene responsible for SSADH has been identified, with many mutations in these patients. Prenatal diagnosis can be based on evaluation of GHB accumulated in amniotic fluid, measurement of enzyme activity in cultured amniocytes, or molecular analysis on chorionic villi DNA.

**Pathophysiology**

The disorder results in accumulation of GHB and GABA coupled with low glutamine levels in the CSF of affected patients. GHB is a neuropharmacologically active compound that may play a role in the brain as a neurotransmitter or neuromodulator. In physiological concentrations, GHB acts at the GHB-receptors. In high concentrations, GHB may be responsible for a disruption of the normal balance between glutamatergic excitatory activity and GABAergic inhibition. This imbalance can be due to the agonist effect of GHB at the GABA-receptor and to the uncoupled glutamine and GABA levels. In addition, metabolites formed via the oxidation of GHB can interfere with energy production and create oxidative damage. Finally, GHB alters catecholamine turnover causing increased HVA and 5-HIAA (Pearl et al. 2014).

**Clinical features**

About a hundred cases are known, with a variable clinical phenotype. The most frequent features are delayed motor, language and intellectual development. Muscular hypotonia, areflexia, and nonprogressive ataxia are frequently described. The other signs are seizures, behavioural problems, ocular dyspraxia, macrocephaly, myopathy, choreoathetosis, nystagmus and conjunctival telangiectasia. EEG studies result in nonspecific findings, with various background abnormalities and epileptiform features. Structural neuroimaging may reveal mild cerebral and cerebellar atrophy. MRI studies have regularly revealed bilateral abnormal signals in the globus pallidus, the subcortical white matter and, occasionally, the brainstem and the dentate nuclei. MRS may reveal increased GABA and GABA metabolites (Novotny et al. 2003).

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**Figure 9.19** Metabolism of g-aminobutyric acid (GABA).

GAD, glutamic acid decarboxylase; GABA-T, GABA-transaminase; SSADH, succinic semialdehyde dehydrogenase; GHB-DH, γ-hydroxybutyric acid dehydrogenase.
**Biochemical Diagnosis**

The diagnosis is confirmed by high levels of GABA in plasma, CSF and urine, in association with abnormal urinary excretion of several GHB by-products. In CSF, there is a significant increase in GHB, free GABA and homocarnosine. In addition, the dopaminergic end products are increased.

**Treatment**

The most widely employed treatment has been vigabatrin, the irreversible GABA transaminase inhibitor. However, its long-term efficacy is limited and it may be contraindicated due to retinal toxicity. Other agents have been investigated in knockout mice models. Benzodiazepines may be useful to control anxiety and aggressiveness. Sodium valproate to control seizures is contraindicated as it may inhibit any residual SSADH enzyme activity.

**Nonketotic Hyperglycinemia (NKH)**

Nonketotic hyperglycinemia (NKH) or nonketotic glycine encephalopathy is an inborn error of amino acid catabolism in which large amounts of glycine accumulate in body fluids. The classic phenotype is a life-threatening illness that develops in the neonatal period, during which most patients die. Survivors have severe intellectual disability and seizures. Atypical variants with variable age at onset and clinical manifestations have less severe prognosis. Rare patients may present a transient neonatal form characterised by biological normalisation (Hoover-Fong et al. 2004; Swanson et al. 2015).

**Pathogenesis of NKH**

Although the mechanism underlying the neurological dysfunction is not fully understood, glycine itself has an important role in the pathogenesis. Glycine is an inhibitory neurotransmitter whose receptors are mainly located in the spinal cord and brainstem. These glycine receptors are specifically antagonised by strychnine and competitively inhibited by benzodiazepines. This inhibitory neurotransmission can explain hypotonia and apnoea. Another strychnine-insensitive site associated with the NMDA receptor plays a major role in excitatory transmission in the cortex and diencephalon. NMDA-mediated neurotoxicity is markedly potentiated by glycine and excessive activation of NMDA receptors may directly result in neurotoxicity (Hoover-Fong et al. 2004).

**Clinical Features of NKH**

**Classic early-onset phenotype**

This is the most frequently occurring type of NKH. Symptoms may appear from hours postpartum to the first few days of life. Lethargy and muscular weakness appear first. Shallow breathing follows and rapidly yields to apnoeic spells. Affected infants are flaccid and unresponsive to stimuli but often present with erratic myoclonias and subtle partial seizures. The burst-suppression pattern on the EEG though nonspecific, is an important diagnostic feature (Fig. 9.20).

A majority of patients die in this early period. For some infants, episodes of apnoea and respiratory depression are transient difficulties, and they may survive. However, no effective treatment is known, and early survivors invariably develop...
a severe epileptic encephalopathy and die within the first few years of life. They display spastic cerebral palsy, associated in most cases with infantile spasms or less often with partial convulsions. The periodic EEG pattern most often disappears after a few months and changes to atypical hypsarrhythmia or multifocal epileptic discharges.

**Atypical cases of NKH**

There are three major types: neonatal, infantile, and late-onset (Dinopoulos et al. 2005). The presentation of the neonatal type is similar to that of classic NKH but the psychomotor development is better.

The infantile type is the most frequent presentation of atypical NKH. It can be easily misdiagnosed as a static encephalopathy. After a neonatal period that may be uneventful, these children have developmental delay that can progress to moderate or profound intellectual disability (60% of cases). Most have some upper motor neuron signs, poor fine motor coordination, expressive speech deficit, hyperactivity and aggressive behaviour. About 50% develop seizures of any type. An acute deterioration induced by intermittent febrile illness or trauma has been described in some patients with lethargy, hypotonia, ataxia, and seizures that are often difficult to control, or unusual symptoms such as myoclonic jerks, abnormal twitching movements, agitated delirium, chorea, ataxia and vertical gaze palsy.

The late-onset form is very rare and more heterogeneous. The presentation is after the second year of life and even in adulthood, mainly with mild cognitive decline and behavioural problems. In a few cases, spinocerebellar degeneration with optic atrophy and neuropathy has been described. The cause of the hyperglycinaemia in these late-onset cases is uncertain, since they all lack enzymatic or genetic confirmation.

MRI shows progressive cerebral atrophy and delayed myelination of the supratentorial white matter. Agenesis or hypoplasia of the corpus callosum is a frequent sign. There is a high signal in the pyramidal tracts, middle cerebellar peduncles, and dentate nuclei. Serial diffusion-weighted and diffusion tensor imaging (DWI, DTI) show increased T2-signal intensity and restricted diffusion consistent with myelinopathy, mainly in the brainstem (Mourmans et al. 2006).

The high peak of glycine individualised on proton MRS allows non-invasive measurement of glycine concentration in the brain in classic NKH (Dinopoulos et al. 2005).

**Biochemical basis of NKH**

Glycine is implicated in numerous biochemical reactions, among which glycine–serine interconversion appears to be the most important for maintaining glycine homeostasis. This reaction involves two reversible enzymatic steps, one subserved by serine hydromethyltransferase, the other by the glycine cleavage system. This last step serving the catabolism is defective in NKH. The glycine cleavage system (GCS) is a mitochondrial enzyme complex made of four individual constituents. These are a P-protein (pyridoxal phosphate-dependent glycine decarboxylase, [GLDC]), a T-protein (tetrahydrofolate requiring aminomethyltransferase, [AMT]), an H-protein (glycine cleavage system hydrogen carrier protein, [GCSH]), containing lipoic acid), and an L-protein (lipoamide dehydrogenase). These four specific proteins allow the degradation of glycine in the liver, kidney, and brain.

The diagnosis is confirmed by the finding of elevation of glycine (control values 125–320μmol/L) (Korman and Gutman 2002). Glycine levels should be measured simultaneously in plasma and in CSF (glycine control values <10μmol/L). In NKH, all other amino acids are unremarkable, remaining within normal values. The diagnosis of NKH is based on a finding of either an increased absolute value of glycine in CSF or an increased CSF to plasma glycine ratio (control values <0.02). In classic neonatal NKH this ratio is very high (>0.08).

Secondary hyperglycinaemia with inhibition of the glycine cleavage system is due to accumulation of several metabolites (for example organic acids, sodium valproate). The clinical setting and a rapid screening of urine organic acids and blood acylcarnitines profile would exclude most other metabolic disorders. Definitive diagnosis relies on enzymatic studies on liver or transformed lymphoblasts in classic forms without residual activity. Atypical and transient forms may have normal activity in lymphoblasts and should have their enzymatic activity measured in liver and/or extensive molecular analysis for diagnosis.

Most patients with the neonatal form of the disease have a very low GCS activity and late-onset patients have some residual activity. About 75% of patients with NKH have a defect in the P-protein, and the remainder have a defect in the T-protein. L- or H-protein deficiencies are apparently very rare (Van Hove et al. 2005).

**Genetics of NKH**

NKH is transmitted as an autosomal recessive trait. Mutations are found in the genes encoding AMT, GLDC, and GCSH (Kure et al. 2006).

**Treatment of NKH**

Therapeutic approaches including dopamine receptor agonists, monoamine oxidase inhibitors, antiepileptics and serotoninergic agents give modest or transient improvement in many patients, while side effects with dystonic and dyskinetic reactions are frequent. However, early treatment has resulted in better outcome in young patients (Pons et al. 2004).

Treatment with high-dosage sodium benzoate is directed towards reducing plasma and CSF glycine levels. Dextromethorphan, ketamine and tryptophan would antagonise the excitatory effect of glycine on NMDA receptors. They all have been used in isolation or in combination without consistent improvement (Dinopoulos et al. 2005; Korman et al. 2006).
SERINE DEFICIENCY SYNDROMES

Serine deficiency syndromes are rare autosomal recessive disorders due to defective synthesis of the amino acid L-serine. So far three disorders have been described: 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency, 3-phosphoserine phosphatase (3-PSP) deficiency and phosphoserine aminotransferase deficiency (3-PSAT). All result in a severe encephalopathy but are potentially treatable (de Koning et al. 2000, de Koning 2006).

BIOCHEMICAL BASIS

L-serine can be derived from different sources. However, its biosynthesis from 3-phosphoglycerate is a predominant route, notably in the CNS. In the L-serine synthetic pathway, 3-phosphoglycerate is converted to L-serine in three consecutive steps. The two disorders described here concern the first and third steps (see Fig. 9.18) and result in important defective brain metabolism. In situ, L-serine is the precursor for the synthesis of the neurotransmitter L-glycine and the neuromodulator D-serine. The folate metabolite 5, 10-methylene tetrahydrofolate, which is generated along with glycine, is a key metabolite especially for purine and pyrimidine synthesis, and for various methylation reactions. Finally, L-serine is a precursor for the synthesis of phosphoglycerides, sphingolipids and glycolipids.

GENETIC BACKGROUND OF SERINE DEFICIENCIES

3-PGDH deficiency is an autosomal recessive disorder. The 3-PGDH gene is located on chromosome 1q12, and mutations have been identified. Molecular investigation is the only tool for prenatal diagnosis in the absence of enzymatic data in chorionic villi and amniocytes.

PATHOGENESIS OF SERINE DEFICIENCIES

L-serine deficiency is thought to reduce cell proliferation. This hypothesis is sustained by the 3-PGDH knockout mouse model that shows a lethal developmental defect with severe brain atrophy. From the experience with prenatal follow-up and treatment of one patient, it seems that the onset of symptoms occurs after the 27th week of gestation. Within this period, the brain development is marked by glial cell proliferation, neuronal differentiation, dendritogenesis and apoptosis. These late pathological consequences may explain the therapeutic effectiveness with serine supplement.

Clinical Features of Serine Deficiencies

A deficiency in 3-PhosphoGlycerate Dehydrogenase (3-PGDH) mainly affects the CNS. Three clinical phenotypes have been described: a severe infantile phenotype, a milder juvenile type and a late-onset polyneuropathy phenotype.

In the severe form, patients present with congenital microcephaly and intrauterine growth retardation. Severe psychomotor delay develops in the first months of life followed by intractable epilepsy. Seizures can be tonic–clonic in type or flexor spasms in infants. In older children, tonic, atonic, myoclonic, absence and gelastic seizures have been observed. EEGs show either hypsarhythmia or severe multifocal epileptic abnormalities with poor background. Other neurological signs include hyperexcitability, generalised hypertonia, spastic quadriplegia and nystagmus. The most severe end is the Neu-Laxova syndrome, with severe facial dysmorphism, ichthyosis, skeletal anomalies and perinatal lethality. Some children have cataracts, hypogonadism, adducted thumbs, inguinal and umbilical hernias and megaloblastic anaemia (Tabatabaei et al. 2009). On MRI the brain is atrophic with striking lack of white matter, delayed myelination and hypomyelination, only seen in the 3-PGDH deficiency (de Koning et al. 2000).

Milder juvenile forms include children with a normal early development, subsequent moderate developmental delay, atypical absence seizures but no microcephaly. In adolescence they tend to have behavioural problems.

An adult was reported with polynuropathy, congenital cataracts, intellectual disability and a polynuropathy in his thirties (Méneret et al. 2012).

DIAGNOSIS OF 3-PGDH

Low concentrations of serine and, to a variable degree, of glycine in plasma and CSF are the biochemical hallmark of the disease. In plasma, the abnormality can be missed if it has been sampled after the patient has eaten. In contrast, serine levels in CSF are not influenced by meals. Therefore, CSF amino acid analysis is preferable over plasma analysis. Amino acid analysis in urine is not informative. Besides deficiency of serine and glycine in CSF, low levels of 5-methyltetrahydrofolate and low D-serine in CSF folate have been observed with normal neurotransmitter amines. The diagnosis is confirmed by measurement of enzymatic activity in fibroblasts and by molecular analysis.

TREATMENT OF 3-PGDH

Oral L-serine supplementation has been effective to control seizures and to improve spasticity, well-being and behaviour of these patients. High dosages up to 600mg/kg/day in four or six divided doses, are required to normalise the biological abnormalities. If seizures are not controlled, glycine can be added at a dose of 200–300mg/kg/day. In patients treated after their first year of life, little or no progress in psychomotor development was observed. In some patients, a marked increase in the white matter volume and progression of myelination was observed in MRI follow-up. No effect on the psychomotor development is observed if the patient is already symptomatic (de Koning 2006).

A girl diagnosed prenatally was treated in utero with oral L-serine supplementation given to the mother from the 27th
week of gestation. This normalised the fetal head growth and with subsequent postnatal therapy this 3-year-old girl had normal development. In the juvenile presentations results were better with L-serine 100–150mg/kg/day resulting in cessation of seizures.

**Phosphoserine Aminotransferase Deficiency**

Phosphoserine Aminotransferase Deficiency (PSAT) the second defect in serine metabolism, was reported in two siblings (Hart et al. 2007). There is an early presentation with feeding difficulties and intractable seizures. On MRI, there was cerebral atrophy and hypoplasia of the cerebellar vermis and pons, as well as white matter changes. Early treatment within hours of birth resulted in a good outcome (Hart et al. 2007).

3-Phosphoserine Phosphatase deficiency was described in a patient with Williams syndrome.

### OTHER GABA-RELATED DISORDERS

#### Pyridoxine Dependency

Pyridoxine dependency is a rare disease characterised by the occurrence of intractable seizures that are controlled only by the administration of pyridoxine. It is transmitted as an autosomal recessive character.

Pyridoxine dependency is due to a defect of a specific dehydrogenase, antiquitin, required for lysine and pipercolic catabolism in the brain. Defective activity of antiquitin results in accumulation of alpha-aminoadipic-semialdehyde (alpha-AASA) and piperideine-6-carboxylic acid (P6C). This latter compound condenses with pyridoxal phosphate resulting in its inactivation. The antiquitin gene *(ALDH7A1)* has been cloned, and various mutations have been identified in several families (Mills et al. 2006; Plecko et al. 2007; Stockler et al. 2010). This peculiar pyridoxal phosphate deficiency may account for low levels of GABA in brain. The clinical features are described in Chapter 27. The diagnosis can be made by demonstration of elevated levels of urinary alpha-aminoadipic semialdehyde (Bok et al. 2010).

#### Pyridox(am)ine 5′-Phosphate Oxidase Deficiency

In humans, vitamin B₆ is present in various forms, one of which, pyridoxal 5′-phosphate, is the cofactor for numerous enzymes including AADC, glycine cleavage enzyme and threonine dehydratase (see also Chapter 27). In tissues, the conversion of pyridoxine to the active form of vitamin B₆ requires pyridox(am)ine 5′-phosphate oxidase (PNPO). Neonates and infants with a pyridoxine-resistant epileptic encephalopathy can react to pyridoxal phosphate administration. This condition is due to an autosomal recessive defect in PNPO (Mills et al. 2005, 2014). CSF and urine analyses show evidence of secondary deficiencies of the several PLP-dependent enzymes. The CSF concentrations of dopamine and serotonin metabolites are similar to those described in AADC deficiency. In addition, CSF amino acid analysis reveals raised levels of glycine and threonine due to reduced activity of the glycine cleavage system and threonine dehydratase.

#### Glutamine Synthetase Deficiency

Glutamine synthetase (GS) catalyses the conversion of glutamate and ammonia to glutamine. High glutamine synthetase activity is found in liver, brain and muscle. Glutamine has various roles depending on the main functions of the different organs. In the brain, synthesis of glutamine is neuroprotective by the removal of ammonia and glutamate. In addition, glutamine has a prominent role in the GABA shuttle that requires normal activity of glutamine synthetase in glial cells. Two unrelated neonates with glutamine synthetase deficiency have recently been described (Häberle et al. 2005, 2006). Prenatal ultrasonography was abnormal with enlarged ventricles and a paraventricular cyst in one patient and dilatation of the posterior fossa in the other. At birth, both patients were in a very poor condition neurologically, with massive hypotonia and seizures. Brain MRI showed atrophy with an almost complete agyria and paraventricular cysts. One patient had other dysmorphic signs and died at 2 days of age. The second one had developed necrolytic erythema and died at 4 weeks. Metabolic investigations revealed remarkably low levels of glutamine in plasma, urine and CSF. Further studies showed low glutamine synthetase synthase activity and mutations in the glutamine synthetase encoding gene.

#### GABA-T Deficiency and Homocarnosinosis

GABA transaminase deficiency and homocarnosinosis have been described in a few patients (Pearl et al. 2015).

### Urea Cycle Disorders

Patients with urea cycle disorders (UCDs) can present from birth to adulthood with symptoms depending on the degree of the enzyme defect. Hyperammonaemia, the common biological hallmark, clearly has a toxic effect on the CNS. At any age, hyperammonaemia may be responsible for acute toxicity, which can be fatal or result in severe CNS sequelae. In less severe forms, mild and chronic hyperammonaemia may lead to cerebral impairment (Leonard and Morris 2002, Smith et al. 2005).
Biochemical Background
The urea cycle subserves the incorporation of nitrogen, not used for protein synthesis, in urea, the waste nitrogen substrate in mammals. The complete cycle, as illustrated in Figure 9.21, is localised in liver, which specifically has the first three required enzymes. The following steps are expressed both in liver and in other tissues. The urea cycle is also part of the biochemical route for de novo arginine synthesis. Hereditary disorders have been described at each enzymatic step. In addition, a defect of ornithine transport across the mitochondrial membrane causes the hyperammonaemia, hyperornithinaemia, homocitrullinuria (HHH) syndrome. In lysinuric protein intolerance, transport of dibasic amino acids (lysine, arginine, ornithine) across the cell membrane results in urea cycle disruption.

In UCDs, the major biochemical finding is hyperammonaemia. Figure 9.22 outlines the diagnostic approach, which is based on determinations of the acid-base status, plasma and urinary amino acids, and oroticuria. In the case of carbamoylphosphate accumulation (ornithine carbamoyltransferase [OCT] deficiency, lysinuric protein intolerance, HHH syndrome) or overproduction (hyperargininaemia), orotic acid is produced through cytosolic activated pyrimidine synthesis. Definitive diagnosis requires enzymatic assays in appropriate tissues and molecular confirmation.

Genetic Background
The OCT gene is located on the X chromosome. Female heterozygotes have a mosaic of normal and affected liver cells as a result of lyonisation and may present with various clinical manifestations from asymptomatic state to severe chronic symptomatology and unexpected acute metabolic crises occurring at any age. For genetic counselling, screening for carriers is essential. Heterozygotes can be detected by protein load or an allopurinol test and by molecular genetic techniques. All the other UCDs are inherited in an autosomal recessive mode. With the genes for all urea cycle enzymes being characterised, antenatal diagnosis for fetuses at risk rely on molecular investigations in chorionic villus tissue.

Pathophysiology
Ammonia appears to be the major cause of the acute encephalopathy. During acute hyperammonaemia, neurological symptoms appear to be secondary to swelling of astrocytes responsible for cerebral oedema and alteration of cerebral
blood flow. Astrocyte swelling is thought to be due to the intracellular osmotic effect of glutamine, whose increased concentrations are evidenced both in the CSF and by MRS in patients during hyperammonaeic encephalopathy. Some manifestations of chronic hyperammonaemia such as anorexia, vomiting and sleep disturbances might be due to increased brain uptake of tryptophan and thus increased brain serotonin turnover (Gropman and Batshaw 2004).

Neurotoxic effects of the other accumulated metabolites such as citrulline and argininosuccinate are still in debate. Arginase deficiency is a disorder characterised by progressive spastic paraparesis and accumulation of arginine, guanidino compounds and creatine, which are potential neurotoxins (Sin et al. 2015).

**Neuropathology**
Abnormalities due to hyperammonaemia are difficult to differentiate from secondary anoxic lesions. In neonates, neuropathological changes include cerebral haemorrhage, prominent cerebral oedema, and generalised neuronal cell loss. In older children, lesions comprise ulegyria, cortical atrophy, ventriculomegaly and cortical neuronal loss.

**Clinical Manifestations of Urea Cycle Disorders**

**Neonatal-onset forms**
The majority of patients presents with symptoms in the neonatal period. Every UCD may be expressed in the newborn infant, but severe neonatal-onset forms are commonly due to OCT or carbamoylphosphate synthetase deficiencies, citrullinaemia or argininosuccinic aciduria. The most important diagnostic features in neonates are vomiting, hypotonia, lethargy progressing to coma, and seizures developing within

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**Figure 9.22 Flow diagram illustrating the diagnosis of hyperammonaemia.**
CPS, carbamyl phosphate synthetase; ARG, Arginine; NAGS, N-acetylglutamate synthetase; OTC, ornithine trancarbamylase; HHH, Hyperornithinemia-hyperammonemia-homocitrullinemia.
hours or days after a symptom-free period of 24 hours or more. Severe hyperammonaemia (>700µmol/L) and respiratory alkalosis are the characteristic biological signs leading to specific biochemical investigations: amino acid chromatography and urinary orotic acid levels. Severe CNS depression and cardiorespiratory failure result in death. Cerebral imaging reveals cerebral oedema during the acute phase. In survivors of prolonged coma, changes observed months later include ventriculomegaly, white matter lesions and cerebral atrophy (Takanashi et al. 2003; Gropman and Batshaw 2004).

Late-onset forms
An increasing number of patients are diagnosed later in childhood or even in adulthood. Whatever the defect, most of the clinical symptomatology is secondary to hyperammonaemia, but some additional signs may indicate specific disorders.

Symptomatology Common to All Hyperammonaemias
Acute hyperammonaemia may be responsible for variously associated signs such as episodes of lethargy and ataxia, coma with infrequent seizures, recurrent vomiting or altered cognitive state manifested by irritability, agitation, incoherent speech and confusion. Such episodes are often associated with vomiting, high protein intake or intercurrent infections, catabolic states although, not infrequently, there is no overt cause. Mild crises abate with cessation of protein intake. Severe or persistent hyperammonaemia can be responsible for severe cerebral oedema, which can progress to diffuse or localised cortical or subcortical atrophy, and diffuse grey and white matter hypodensity. Proton MRS may reveal decreased myoinositol and choline concentrations, and increased glutamate plus glutamine peaks. Central pontine myelinolysis is a rare complication that leads to an unusual neurological course. These features can to some extent be reversible, and their severity is usually correlated with the duration of hyperammonaemic coma. Such acute manifestations often lead to the misdiagnosis of encephalitis, cerebral tumour or vascular accident. Hepatomegaly and hepatic failure are frequent, and Reye-like syndrome or drug toxicity are often discussed. Chronic hyperammonaemia may result in protein avoidance, anorexia, vomiting and failure to thrive, mimicking various food intolerances. Hyperactivity, nocturnal episodes of restlessness, destructive behaviour and progressive intellectual disability are often misdiagnosed as psychiatric problems.

In both acute and chronic forms, diagnosis is based on plasma ammonia levels. Marked hyperammonaemia accompanies acute episodes. In milder forms, ammonia levels may be normal after an overnight fast, so determinations should be made following protein intake (see Fig. 9.22).

Specific Clinical Signs of Urea Cycle Disorders
Argininosuccinic aciduria and some cases of citrullinaemia may present with brittle hair, trichorrhaxis nodosa and prominent hepatomegaly.

In arginase deficiency the major features include early progressive spastic paraparesis, associated with loss of cognitive skills. Seizures, ataxia and athetosis can be additional signs. This progressive neurological impairment is often accompanied by minor signs of chronic hyperammonaemia, while acute episodes of metabolic decompensation are rarely noted (Scaglia and Lee 2006).

HHH syndrome may present in the neonatal period or late in childhood with mild symptoms of hyperammonaemia associated with muscle hypotonia. Progressive spastic paraparesis that commonly develops during adolescence can arise earlier in children treated with high doses of arginine supplementation. Cognitive development varies widely from normal intelligence to severe intellectual disability.

Lysinuric protein intolerance presents in infants with anorexia, recurrent vomiting, lethargy, growth failure, muscle hypotonia, hepatosplenomegaly, pancytopenia and osteoporosis. Drowsiness or coma often results from forced feeding with high-protein foods.

Treatment of Urea Cycle Disorders
Neonatal-onset forms and some acute late decompensations require rapid exogenous detoxification procedures. Long-term therapy aims at limiting the endogenous and exogenous nitrogen load, at supplying deficient metabolites (e.g. citrulline, arginine, ornithine, aspartate), and at increasing the disposal of nitrogen by means other than urea formation.

Nitrogen load is reduced by restricting protein intake and promoting anabolism. Disposal of ammonia by means of benzoate and phenylacetate, which conjugate respectively with endogenous glycine and glutamine, helps eliminate waste nitrogen as hippurate and phenylacetylglutamine. Arginine becomes an indispensable amino acid for patients affected with OCT and carbamoylphosphate synthase that require supplemental arginine. Conversely, treatment of hyperargininaemic patients is based on an arginine-controlled diet. In other disorders, chronic supplementation with high doses of arginine may result in toxicity. The rare patients affected with N-acetyl-glutamate synthetase defect (NAGS), as well as some patients with partial carbamoylphosphate synthetase, can be treated with N-carbamoyl glutamate supplementation.

Therapy has to be specifically tailored to the specific UCD, and each individual patient must be evaluated for metabolic profile before an optimal therapy can be instituted. Despite careful management, liver transplantation may represent the only available therapeutic approach for children with severe recurrent acute decompensations (Silva et al. 2013). Only patients who are NAGS deficient can be successfully treated with N-carbamoyl glutamate supplementation without specific diet.
The metabolic pathways involved in glycolysis, neoglucogenesis, glycogen synthesis, and metabolism of galactose and fructose are discussed here. Most of these diseases have more general symptoms, and neurological symptoms may arise as a result of deranged metabolism such as hypoglycaemia.

**GLYCOGEN STORAGE DISEASES**

This group of diseases is involved in deranged synthesis or degradation of glycogen and is often associated with hepatomegaly. Most involve liver dysfunction, with hypoglycaemia as a consequence. An exception is the glycogen myopathies which will be discussed in Chapter 26.

There are more than 12 different enzyme deficiencies in this pathway. Most can be studied in leukocytes, in others a liver biopsy is necessary. Treatment includes frequent meals and uncooked corn-starch at bedtime (0.5–1g/kg).

**DISORDERS OF PENTOSE METABOLISM**

The pentose phosphate pathway generates nicotinamide adenine dinucleotide phosphate (NADPH) (required for a number of anabolic reactions) and pentoses (5-carbon sugars). A number of single deficiencies are described.

**Ribose-5-Phosphate Isomerase Deficiency**

There are a few patients described with intellectual disability and epilepsy, developing ataxia and neuropathy and demonstrating on MRI extensive abnormalities in white matter (Wamelink et al. 2008).

**Transaldolase (TALDO) Deficiency**

This disease manifests as a severe, early-onset multisystem disease with hepatosplenomegaly, thrombocytopenia, anaemia, bleeding diathesis, liver failure and tubulopathy. Deafness has been described (Eyaid et al. 2013).

Increased polyol concentrations with high concentrations of erythritol, ribitol, arabitol, sedoheptitol, perseitol, sedoheptulose and sedoheptulose-7-phosphate are found in the urine. The disease can be confirmed by molecular analysis of the TALDO gene (Tylik-Szymanska et al. 2014).

Disorders of galactose and fructose metabolism do not present with major neurological features if treated with an adequate diet. In galactosaemia, verbal apraxia can occur in some patients not related to diet control.

**TRANSPORTER DEFECTS**

**GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY SYNDROME**

The disease leads to impaired glucose transport to the brain resulting in brain energy deficiency.

The initial glucose transporter type 1 deficiency syndrome (GLUT1DS) clinical description included young infants with intractable seizures needing to be treated early and with a successful outcome with a ketogenic diet. Besides intractable seizures, other phenotypes are also described in life such as early ocular movement disorders or early-onset absence seizures, a non-classic phenotype with intellectual disability or a movement disorder without epilepsy (Leen et al. 2010).

Seizures in GLUT 1 deficiency can be of all types ranging from severe myoclonic–atonic seizures, through generalised tonic–clonic, absences, and nocturnal or early morning seizures (see also Chapters 16 and 19).

**Diagnosis**

The sole biochemical abnormality is a very low CSF glucose with a low CSF–blood glucose ratio of less than 0.4 and low CSF lactate. The diagnosis can be confirmed by analysis of the SLC2A1 gene. Most patients carry heterozygous de novo mutations but autosomal dominant transmission has also been identified.

A ketogenic diet (Klepper et al. 2005; Klepper 2012) or a modified Atkins diet is the treatment of choice, to provide ketones as an alternative fuel for the brain. However, persistence with the diet can be difficult to sustain. Other diets such as low-index glucose and corn-starch to keep glucose levels constant have been tried more recently (Almuqbil et al. 2015).

**CEREBRAL FOLATE TRANSPORTER**

**Thiamine Transporter-2 Deficiency**

Thiamine transporter-2 deficiency is caused by mutations in the SLC19A3 gene. Early administration of thiamine and biotin has a dramatic and immediate clinical effect (see also biotin-responsive basal ganglia disease in the Biotin Metabolism section).

In patients, free-thiamine was remarkably reduced in the CSF of five SLC19A3 patients before treatment. Thiamine supplementation led to clinical improvement in patients early treated and restored thiamine values in fibroblasts and CSF.

**Riboflavin Transporter Deficiency**

Riboflavin transporter deficiency neuronopathy is characterised by motor neuronopathy (manifest as proximal and distal limb weakness, often with severe distal wasting and breathing
problems due to paralysis of the diaphragm), sensory neuropathy, and cranial neuropathy (manifest as optic atrophy, sensorineural deafness, and bulbar palsy). Onset is usually in infancy or in childhood before the age of 8 years.

Several transporters have now been described. RFVT2 (SLC52A2) and RFVT3 (SLC52A3) present with Brown-Vialetto-van Laere syndrome (Bosch et al. 2011; Foley et al. 2014).

**GENETICS**

Riboflavin transporter deficiency neuropathy is inherited in an autosomal recessive manner.

### MITOCHONDRIAL MEDICINE

#### RESPIRATORY CHAIN DISORDERS

The respiratory chain is the main biochemical system used to yield aerobic energy in all eukaryotic organisms. In humans, its dysfunction is responsible for numerous and highly variable mitochondrial diseases that all have in common defective ATP production along with insufficient energy provision in one or several tissues or organs. This effect may vary from one tissue to another, according to their dependence on phosphorylative oxidation. Muscle tissue in general is particularly sensitive to diminished ATP supply, resulting in various symptoms such as ptosis, ophthalmoplegia, muscle weakness, exercise intolerance, and cardiomyopathy. The nervous system is also highly susceptible, resulting in encephalopathy, sensorineural signs and peripheral neuropathies. Other tissues may also be affected depending on the extent and severity of the defect. Kidney, liver, pancreas and gastrointestinal tissues are the most often implicated organs. Clinically, mitochondrial disorders are extremely heterogeneous. They may affect a single organ or tissue but most often cause multisystemic disorders, among which syndromic conditions have been described for years (Zeviani and Di Donato 2004; DiMauro and Hirano 2005).

**Functional Organisation of the Respiratory Chain**

The mitochondrial respiratory chain is a group of five enzyme complexes embedded in the inner mitochondrial membrane. Each complex is composed of multiple polypeptide subunits and prosthetic groups (Table 9.7). In addition, the respiratory chain contains two electron carriers, coenzyme Q<sub>10</sub> and cytochrome c. The respiratory chain is especially organised to accept electrons from NADH and FADH<sub>2</sub>, the reducing factors generated from the intermediary metabolism (Fig. 9.23). These electrons flow down the respiratory chain to molecular oxygen to produce water. Simultaneously, the energy liberated during this flux is used by complexes I, III and IV to pump protons (H<sup>+</sup>) out of the mitochondrial matrix into the intermembrane space. Complex V allows protons to flow back into the mitochondrial matrix and uses the released energy to synthesise ATP from ADP and inorganic phosphate (DiMauro and Schon 2003).

**Genetic Background**

Mendelian mitochondrial defects can affect five components of mitochondrial biology (DiMauro et al. 2013): subunits of respiratory chain complexes (direct hits); mitochondrial assembly proteins; mtDNA translation; phospholipid composition of the inner mitochondrial membrane or mitochondrial dynamics. A sixth category – defects of mtDNA maintenance – combines features of Mendelian and mitochondrial genetics.

Human mtDNA contains the genes for 13 OXPHOS (respiratory chain, electron transport chain) subunits, as well as for the 22 transfer RNAs (tRNAs) and the two ribosomal RNAs (rRNAs) required for the intramitochondrial synthesis. The remaining structural proteins are encoded by nDNA.

nDNA also encodes hundreds of additional factors required for subunit protein expression, transport, translation, elongation and assembly as well as for mtDNA synthesis, expression and stabilisation. In addition, mitochondria are not static organelles and other nuclear encoded factors govern their mobility, fission and fusion. In total, it is estimated that respiratory chain functions require about 1000 separate proteins, mostly encoded by nDNA, with mutations potentially responsible for Mendelian inherited diseases.

In consequence, mitochondrial diseases may be caused by mutations in genes from either mtDNA or nDNA. However, clinically indistinguishable disorders may be caused by separate mutations in different genes on different genomes. Conversely, one specific mutation may result in a number of distinct clinical symptoms in different individuals even in one family.

**Diagnosis/Testing**

A pattern of blood acylcarnitines and organic acids in urine suggests multiple acyl-CoA dehydrogenase deficiency can can be confirmed by the demonstration of mutations in either SLC52A2 or SLC52A3.

**Management**

High-dose oral supplementation with riboflavin between 10 and 50mg/kg/day improves symptoms and signs on clinical examination, and normalises acylcarnitine levels.
Mutations in mtDNA

These include point mutations and large-scale rearrangements. Point mutations were first described in genes encoding various tRNAs resulting in wide spread impairment of protein synthesis. They usually are heteroplasmic, only maternally inherited and associated with a striking variety of multisystem disorders. More than 260 pathogenic mutations and 120 large-scale rearrangements (single mtDNA deletions) have been identified in the mtDNA.

Point mutations in protein-coding genes affect one of the mitochondrial encoded subunits in complex I (ND), complex III (Cyt b), complex IV (COX) or complex V (ATPase6). ND5, which encodes the subunit 5 of complex I, is the site of numerous point mutations associated with various multisystem disorders such as Leigh encephalopathy.

Large-scale rearrangements consist of a single deletion/duplication in mtDNA. They differ in size from one patient to another and delete several protein-coding and tRNA genes. They tend to arise spontaneously and are heteroplasmic. However, some cases may be maternally inherited with variable phenotypic expression between the affected female and her offspring.

Mutations in nuclear genes

These include mutations in genes that encode complex subunits, ancillary proteins, protein factors required for intergenic signalling, and protein factors necessary for membrane maintenance, phospholipid of inner mitochondrial membrane, and for mobility of mitochondrion. These mutations are responsible for Mendelian autosomal recessive, dominant or X-linked inherited diseases.
Mutations in genes encoding respiratory chain subunits are increasingly recognised. Various mutations in genes encoding subunits of complex I (NDUFS and NDUFV) and complex II (SDHA) are mainly responsible for Leigh or Leigh-like syndromes. Mutations in genes encoding enzymes implicated in the biosynthetic pathway of CoQ have been identified. They include PDSS2, PDSS1, SCO1, CoQ6, ADCK3 and CoQ9 giving rise to five clinical syndromes with variable tissue affection (Emmanuele et al. 2012; Scalai et al. 2013).

The nuclear gene (BCS1L) involved in complex III deficiency was the first reported assembly defect. Mutations are responsible for an early and severe multisystem disorder first described in Turkish patients and also called GRACILE syndrome (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death) in Finland, where it has a high incidence. Mutations in the COX-assembly gene SURF1 are frequently associated with Leigh syndrome due to complex IV deficiency. Other mutations in seven more COX-assembly genes (SCO1, SCO2, COX10, COX14, COX5, CoA5, FAM36A and TACO1) have been described in patients affected with Leigh-like encephalopathy and preferentially affecting the brain. Some, such as mutations in COX10, COX5 COA5, have more severe cardiomyopathy whereas mutations in SCO1 cause hepatopathy (DiMauro et al. 2013).

A group of COX-deficient Leigh syndrome patients is due to mutations in the LRPPRC gene which has been described in French Canadian families. Patients with muscle COX deficiency and ethylmalonic aciduria have mutations in the ETHE1 gene. Dysfunction of ETHE1 results in excessive accumulation of hydrogen sulphide which is a powerful COX inhibitor (Tiranti et al. 2009).

Finally, mutations in the ATP12 gene impair the assembly of complex V and are responsible for a lethal encephalomyopathy (De Meirleir et al. 2004).

**Mutations in genes encoding factors for mtDNA maintenance**

**Defects in the replication machinery**

The replicative machinery includes the catalytic subunit of polymerase (POLG) and the replicative helicases Twinkle (encoded by PE01 and DNA2) (Horvath et al. 2006; Ronchi 2013).

Depending on which of the three POLG domains (polymerase, exonuclease or linker region) the clinical phenotype ranges from severe hepatocerebral disorder (Alpers syndrome) to adult-onset autosomal dominant or autosomal recessive progressive external ophthalmoplegia, parkinsonism and other clinical phenotypes including sensory ataxic neuropathy, dystarhtia and ophthalmoparesis (SANDO) or mitochondrial recessive ataxic neuropathy.

Two others genes are responsible for autosomal dominant progressive external ophthalmoplegia (PEO) and multiple DNA deletions in muscle, ANT1, encoding an isoform of the adenine nucleotide transporter and POLG2.

**Defects involving the dNTP pool**

These Mendelian disorders with qualitative (deletions) or quantitative (depletion) alterations in mtDNA result from an imbalanced supply of deoxyribonucleotides to the mitochondrion (Alberio et al. 2007). Six genes have so far been implicated in the pathogenesis of mitochondrial depletion syndromes (MDS) namely, the thymidine kinase (TK2) gene in myopathic forms, the beta-subunit of the ADP-forming succinyl-CoA synthetases (SUCL2, SUCLG1 and RRM2B) in encephalomyopathic MDS, and deoxyguanosine kinase (DGuoK) in hepatocerebral MDS.

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), is due to mutations in TYMP (Hirano et al. 2005) involved in pathways for the synthesis of deoxyribonucleotides (ANT1 and RRM2B).

**Defects in mtRNA translation**

The translation process comprises several steps requiring initiation factors (IF2 and IF3), elongation factors (EF-Tu, EF-Ts and EFG1), encoding an elongation factor, releases factors (eRF1 and ICT1n, as well as several translational activators TACO1 and LRPl30) and specific tRNA base modifiers (TRMU and PUS1). The PUS1 gene, which encodes the mitochondrial enzyme pseudouridine synthetase, is associated with myopathy, lactic acidosis and sideroblastic anaemia (MLASA).

Mutations in genes encoding mRNA polyadenylation factors, ribosomal proteins, ribosomal protein assembly factors, aminocyl-tRNA synthetases and many other genes have been recently described.

**Defects of the mitochondrial inner membrane lipid milieu**

Among these defects is Barth syndrome (X-linked mitochondrial myopathy, cardiomyopathy, neutropenia, and 3-methyl glutaconic aciduria) with low cardiolipin levels due to mutations in TAZ, the tafazzin gene. Cardiolipin, a major phospholipid component of mitochondrial inner membrane, modulates the activities of several respiratory chain complexes.

Sengers syndrome primarily affects heart and muscle and is associated with congenital cataracts. Using whole exome sequencing the responsible gene, AGK, encoding acylglycerokinase was found.

The mitochondrial-associated endoplasmic reticulum membrane also has several functions important in energy metabolism. A new form of congenital muscular dystrophy (CMD) with multisystem involvement and characteristic mitochondrial structural changes, due to choline kinase beta (CHKB) gene defects has been characterised by intellectual disability, autistic features, ichthyosis-like skin changes, and dilated cardiomyopathy (Haghighi et al. 2014).

Altered MIM phospholipid composition was also found in MEGDEL 3-methyl glutaconic aciduria, deafness, Leigh syndrome due to mutations in the SERAC1 gene (Wortmann et al. 2012).
Defects of mitochondrial dynamics
Defects in proteins required for mitochondrial mobility have been described in autosomal dominant hereditary spastic paraplegia with mutations in one kinesin gene (KIF4). Defects in (dynamin) the protein required for mitochondrial fusion have been reported in autosomal dominant optic atrophy (OPA-1) and in an autosomal dominant variant of Charcot–Marie–Tooth type 2A with defects in mitofusin 2 (MNF2).

Biological Features and Diagnostic Tests
In paediatric patients, the majority (90%) of proven respiratory chain defects present with raised lactate in blood, urine or CSF, often accompanied by a raised lactate to pyruvate ratio signifying a change in cellular redox state. Cerebral or CSF, often accompanied by a raised lactate to pyruvate ratio signifying a change in cellular redox state. Cerebral MRS is a non-invasive and useful means to evaluate lactate accumulation in brain. In addition, it allows an easy diagnosis of the rare complex II deficiency by the presence of an abnormal peak of succinate (Brockmann et al. 2005). Some patients do not display lactic acidosis at rest, depending on the severity of the energy defect, the organ involvement, and the consequence of the primary defect on the oxidation rate. In some cases, lactic acidosis can spontaneously be precipitated by infection or functionally provoked by a glucose loading test. Those patients most affected with exercise intolerance may develop a severe hyperlactacidaemia after non-strenuous exercise. However, lactic acidosis is not an absolute requisite for diagnosis, especially in late childhood or adolescence. Apart from the usual lactaturia, rare patients have abnormal urinary excretion of Krebs cycle intermediates such as fumarate, malate, alpha-ketoglutarate, succinate or 3-methylglutaconic acid. Mild methylmalonic aciduria has been found associated with a SUCLA2 gene mutation responsible for mtDNA depletion syndrome (Carrozzo et al. 2007). Ethylmalonic aciduria is indicative of ethylmalonic encephalopathy, a condition harbouring marked complex IV deficiency in muscle. High levels of thymidine, deoxyuridine and uracil in blood and urine are indicative of MNGIE with thymidine phosphorylase deficiency. Carnitine deficiency in serum and muscle may reflect inefficient fatty acid oxidation. Serum creatine kinase values can be high in myopathic forms of mtDNA depletion syndrome.

MRS may be useful in children over 8 years of age, adolescents and adults. Measurement of the phosphocreatine/inorganic phosphorus ratio during muscle exercise may indicate an ATP-synthesis defect. An aerobic forearm test can raise a suspicion of a mitochondrial disorder when failure of O2 uptake occurs during the test. In patients with a clearly defined clinical syndrome, it may be possible to confirm the diagnosis with a simple molecular genetic test on DNA extracted from blood. Good examples of this are MNGIE (TYMP), the infantile encephalohepatop athy (DGUOK) and infantile encephalopathy (BCS1L). Investigation in the remaining patients is more difficult, especially because pathogenic mutations may not be detectable in blood. An mtDNA heteroplasmic mutation test can sometimes be more sensitive in urine.

A histochemical examination on muscle biopsy using Gomori, cytochrome c oxidase and succinate dehydrogenase (SDH) stains that revealed mitochondrial proliferation and mosaicism would be suggestive of mtDNA mutations and complex II or IV deficiencies.

Biochemical investigations include two main, and non-exclusive, procedures using mitochondria-enriched fractions from fresh tissue for polarographic studies or using frozen tissue for analysis of individual respiratory chain enzyme activities by spectrophotometry. For this purpose, skeletal muscle biopsy specimens are most often used. However, specific studies can be performed on fibroblasts, blood cells, liver, kidney or brain. In principle, the relevant tissues is the one that is clinically affected, i.e. investigation on a liver sample is recommended in hepatoneuropathy. In cases with dubious biochemical results when the clinical level of suspicion is high, investigations in several tissues should be performed.

A structured approach to molecular investigations could include a southern blot of muscle mtDNA looking for mtDNA rearrangement and sequencing of the mtDNA. Further molecular screening, guided by the clinical phenotype, family history and results of biochemistry would help to define an increasing number of pathologies allowing proper genetic counselling.

The major challenge to the accurate diagnosis of mitochondrial disease is the absence of a definitive biomarker that characterises the disorder in all patients. To aid the interpretation, diagnostic schemes for infants and children have been established to categorise the likelihood of mitochondrial disease in a given patient as definite, probable, possible or unlikely (Wolf and Smeitink 2002). Recently introduced, screening panels of mitochondrial genes and whole exome generation sequencing may prove faster in getting to a diagnosis.

Clinical Features of Mitochondrial Disorders
Due to the complexity of mitochondrial genetics and biochemistry, the clinical manifestations of these disorders are extremely heterogeneous. They range from lesions in a single tissue or organ such as the optic nerve in Leber hereditary optic neuropathy, to more widespread lesions including myopathies, encephalomyopathies, cardiomyopathies or complex multisystem syndromes with onset ranging from the neonatal period to adulthood. Certain associations have long been identified as distinct entities such as Kearns–Sayre syndrome (KSS), myopathy, encephalopathy, lactic acidosis and stroke-like (MELAS), myoclonic epilepsy with ragged red fibers syndrome (MERFF), neurogenic weakness, ataxia and retinitis pigmentosa (NARP), Leigh syndrome and Alpers disease. However, not all patients with respiratory chain disorders may be so easily categorised, and many overlaps between clinical syndromes have been documented. Consequently, respiratory chain disorders must be considered in patients presenting with an unexplained and progressive association of neuromuscular and non-neuromuscular symptoms (DiMauro and Schon 2003; Robinson 2006).
**Myopathic Forms of Respiratory Chain Disorders**

Myopathic forms are characterised by progressive weakness of the limbs with variable exercise intolerance, muscle pain, breathlessness, tiredness and nausea. Symptoms may appear within the first 2 years of life, with hypotonia and delayed motor skills, or later in childhood, adolescence or adulthood. Patients can die from early cardiorespiratory failure or remain stable for years. Lactataemia at rest can be normal or mildly increased. Short aerobic exercises can provoke severe lactic acidosis. Except in very young children, morphological and histochemical abnormalities in biopsied muscle are often characteristic. These isolated myopathic forms are associated with mtDNA point mutations in genes encoding subunits of complexes I, III (cytochrome b) or IV. A defect due to mutations in the cytochrome b gene is probably the most characteristic example as it mainly presents with isolated and progressive myopathy and exercise intolerance.

Primary CoQ_{10} deficiency, an autosomal recessive condition with a large clinical spectrum, has a pure juvenile myopathic form with exercise intolerance and eventually myoglobinuria. Other presentations are: (1) encephalomyopathy with brain involvement and recurrent myoglobinuria; (2) severe infantile multisystemic disease; (3) cerebellar ataxia; (4) Leigh brain involvement and recurrent myoglobinuria. Other presentations are: (1) encephalomyopathy with isolated and progressive myopathy and exercise intolerance.

Primary CoQ_{10} deficiency, an autosomal recessive condition with a large clinical spectrum, has a pure juvenile myopathic form with exercise intolerance and eventually myoglobinuria. Other presentations are: (1) encephalomyopathy with brain involvement and recurrent myoglobinuria; (2) severe infantile multisystemic disease; (3) cerebellar ataxia; (4) Leigh syndrome with ataxia and deafness. These patients with ragged red fibres and undetectable CoQ_{10} in tissues are amenable to treatment with high doses of exogenous CoQ_{10}.

The myopathic presentations of cytochrome c oxidase (complex IV) deficiency include three main variants: a fatal infantile myopathy, a benign reversible infantile myopathy, and a late-onset (adult) myopathy. Both fatal and benign forms present in newborn infants with severe and generalised weakness, respiratory distress and lactic acidosis. Patients with the fatal form usually die of respiratory failure within months. Some remain more stable and some patients with a benign form improve spontaneously despite initial severe weakness, and are usually normal by early childhood. (Horvath et al. 2009). Some severe forms mimicking spinal muscular atrophy have been described with mutations in the nuclear encoded SCO2 gene, with the mitochondrial encoded COX1 gene, and with mtDNA depletion due to mutations in the nuclear gene encoding thymidine kinase 2 (FK2).

**Multisystem Forms of Respiratory Chain Disorders**

These involve mainly the CNS and present in the neonatal period or later in childhood, adolescence or even in adulthood.

**FATAL INFANTILE FORM**

This features neonatal lactic acidosis with hypotonia, seizures and respiratory distress, and results in death within a few months. As in complex IV deficiency, renal, cardiac and hepatic involvement may be seen. Severe hyperlactataemia is present, while morphological studies of muscle can be normal or reveal a nonspecific lipid–glycogen storage. MRI may show cortical and subcortical atrophy and dysmyelination. This syndrome is frequently, but not exclusively, associated with complex I and complex IV deficiencies.

**PROGRESSIVE ENCEPHALOPATHY/ENCEPHALOMYOPATHY**

Severe encephalopathy may start later in infancy or childhood after a period of apparently normal development. The following manifestations can be present: developmental delay, hypotonia, weakness, ataxia, pyramidal signs, seizures, myoclonia, retinopathy, ptosis, PEO, sensorineural deafness, mild dysmorphism and growth retardation.

Plasma lactate levels can be normal but high CSF lactate and lactaturia are of great diagnostic value. Some patients present with bouts of drowsiness following intercurrent infections during which high plasma lactate levels occur. Ragged red fibres are frequently associated with lipid–glycogen storage. MRI may be normal or reveal cerebral and/or cerebellar atrophy and bilateral hyperdensity in the basal ganglia or white matter abnormalities. Altered EMG, nerve conduction velocities and visual or brainstem evoked potentials can be found. Cases have been described with defects in all respiratory chain complexes due to various point mutations in either the mt- or nDNA. Specific associated neurological signs such as polymicrogyria, or associated visceral signs such as cardiomyopathy, nephropathy or hepatopathy may be helpful to lead to the diagnosis.

**SUBACUTE NECROTISING ENCEPHALOPATHY: LEIGH SYNDROME**

Leigh syndrome is an inherited, progressive, metabolic disease of infancy and childhood. It causes striking neuropathological features of focal, bilateral and symmetrical necrotic lesions associated with demyelination, vascular proliferation, and gliosis in the brainstem, diencephalon, basal ganglia, cerebellum, and occasionally in the white matter (Farina et al. 2002) (Fig. 9.24). The neuropathological changes involve most consistently the brainstem in a bilateral, roughly symmetrical distribution. The lesions are sharply delineated and cut across grey and white matter with preponderance in the former. The pathological complex of Leigh syndrome consists of a marked spongiosis involving mainly the neuropil, while neurons are relatively preserved. White matter lesions include loss of myelin and, eventually, of axons. An intense capillary proliferation with endothelial swelling is an essential feature. Lesions of this type characteristically affect the tegmentum of midbrain and pons, the peri-aqueductal grey matter, the substantia nigra and posterior colliculi, the floor of the fourth ventricle, and the dentate nuclei. Lesions of the basal ganglia, especially the putamen and caudate nuclei, are common (Fig. 9.25). The
Figure 9.24  **Leigh syndrome.** Typical histological appearance of tissues: note sharply demarcated area of marked spongiosis with intense capillary proliferation.

Figure 9.25  **Leigh necrotizing encephalomyelopathy.** Cavitation of both lenticular nuclei. Head of left caudate nucleus is hypodense. There is marked atrophy of head of right caudate nucleus with widening of corresponding frontal horn.
mamillary bodies are only rarely affected, which is important for distinguishing the condition from Wernicke disease in which similar lesions are present but regularly involve these structures.

The clinical manifestations are extremely variable, and the diagnosis is very difficult as no biochemical markers are available in a majority of cases. Some common features such as deterioration with slow recovery following infections, exercise intolerance, poor somatic growth and abrupt changes in respiratory or cardiac rate may suggest the diagnosis of mitochondrial disorder.

In the infantile form, signs usually appear within the first few years of life and consist of hypotonia, failure to thrive, psychomotor regression, pyramidal tract signs, and brainstem and basal ganglia dysfunction. This basal ganglia involvement results in ataxia, abnormal ocular movements such as ptosis or ophthalmoplegia, dystonia or rigidity, and swallowing difficulties. Movement disorders including choreoathetosis, dystonia and sometimes myoclonus are not infrequent. Involvement of the peripheral nervous system is not rare. In a few cases, it may be the predominant manifestation and may simulate Guillain–Barré syndrome. Seizures occur in some patients and may present as infantile spasms. As a whole, the course is often rapidly progressive with alternating periods of remissions and exacerbations. These are often precipitated by infections or fasting. Acute fulminating cases, protracted courses with prolonged periods of stabilisation, and cases with very slow progression have all been recorded.

Later forms are less commonly encountered but may occur throughout childhood and adolescence and well into adulthood. Predominant extrapyramidal manifestations such as dystonia or abnormal movements, hypokinesia and rigidity could be predominant signs. In some cases, mild psychomotor retardation with slight neurological abnormalities may remain unchanged for years until rapid deterioration occurs, sometimes only in adulthood.

Although mostly due to autosomal recessive inheritance, dominant, X-linked and maternal inheritance is also possible. This genetic heterogeneity has been confirmed with the identification of functional or molecular defects in several enzymes involved in energy production, including pyruvate dehydrogenase, pyruvate carboxylase and respiratory chain complexes and mutations in mtDNA. As already described for unidentified encephalomyopathy, some specific clinical, biochemical or genetic features may be associated and lead to the final diagnosis.

In infancy, defects in each respiratory chain complex may present as Leigh syndrome. This presentation is the most common expression of isolated and profound COX deficiency. Associated with peripheral neuropathy, it is mainly due to mutations in the nuclear SURF1 gene. Leigh syndrome is also a usual presentation of complex I deficiency secondary to mutations either in nuclear or in mitochondrial encoded subunits. Associated with hypertrophic cardiomyopathy it can indicate defects in the nuclear encoded subunits (NDF52, NDF54, NDF57 and NDF58). Defects in complex II due to mutations in the SDHA gene are responsible for Leigh syndrome with a peculiar involvement of the white matter and a recognisable peak of succinate on brain MRS (Brockmann et al. 2005). Mutations in BCSIL, an assembly gene for complex III, present in early infancy with a specific combination of Leigh syndrome, liver insufficiency and tubulopathy, while deletions in subunit VII (UQCRB) cause lactic acidosis with hypoglycaemia. Mutations in mitochondrial ATP6 gene producing complex V deficiency are responsible for either a maternal inherited Leigh syndrome when present at high heteroplasmy or neurogenic weakness, ataxia and retinitis pigmentosa (NARP syndrome) at low titres. In addition, early-onset Leigh syndrome can be associated with mitochondrial depletion syndromes such as SUCLA2 and POLG where there is an associated hepatopathy.

Typical abnormalities visualised on MRI are essential for the in vivo diagnosis of Leigh syndrome as they may be more characteristic than the combination of appropriate clinical features with lactic acidosis. Lesions are visible and hyperintense on proton density and T2-weighted images, whereas they are hypointense, and usually less evident, on T1-weighted images. Lesions are mainly found in the brainstem where they affect various structures of the medulla oblongata, the pons and the midbrain. Involvement of the cerebellum is frequent, mainly centred on the dentate nuclei with extension to the surrounding white matter. Basal ganglia, thalami and subthalamic nuclei are a third site. Extensive lesions in the deep cerebral white matter and progressive cerebral atrophy or infarction may be additional features.

**KEARNS–SAYRE SYNDROME**

KSS is usually a sporadic multisystemic disorder characterised by an invariant triad comprising onset before age 20 years, PEO and pigmentary retinal degeneration, plus at least one of the following: heart block, elevated CSF protein content and cerebellar dysfunction (Zeviani and Di Donato 2004). Still other clinical abnormalities are present in many cases, and two constant pathological features have been described: ragged red fibres and spongy degeneration of the brain. The signs and symptoms may progress in various sequences.

Pearson syndrome, which can evolve into KSS with age, is characterised by sideroblastic anaemia in neonates or infants, associated with exocrine pancreatic dysfunction. This syndrome has similar large-scale single deletions/duplications of mtDNA, as seen in KSS.

Children with KSS usually have normal early development. Ptosis and PEO are usually the first neurological manifestation of the disease, often associated with degenerative pigmented retinopathy and sometimes with optic atrophy. The most common neurological feature is a cerebellar syndrome that may become severe. Intellectual disability or regression may be present. Deafness can also develop.
Seizures do not occur, unless there is concomitant hypocalcaemia with hypoparathyroidism. Heart block is a late sign that may be responsible for syncopal episodes or sudden death despite pacemaker insertion. Rarely, congestive heart failure and supraventricular tachycardia are encountered. Associated endocrine disorders may include short stature with growth hormone defect, latent diabetes and hypoparathyroidism. Renal dysfunction often includes a proximal tubular defect, distal tubulopathy, glomerulopathy, and renal failure. Mild lactic acidosis and high CSF protein are typical laboratory findings.

Neuroimaging shows both grey and white matter lesions, most often localised in the brainstem tegmentum, cerebral and cerebellar white matter, and basal ganglia. Calcifications in the basal ganglia or deep white matter are commonly seen. Involvement of the subcortical U-fibres with relative sparing of the periventricular white matter is typical of KSS. However, these classic lesions develop progressively with age, and MRI can be normal in early stages of the disease. An extinguished ERG and abnormal visual evoked potentials may precede ophthalmoscopic evidence of retinopathy. EMG and nerve conduction velocity studies in some cases may indicate peripheral neuropathy or myopathic changes.

Histochemical and electron microscopic studies of skeletal muscle demonstrate ragged red fibres and altered mitochondria. Altered type I fibres lacking histochemical cytochrome c oxidase activity coexist with normal fibres. Eighty per cent of patients with KSS have a single deletion in mtDNA. Most often the KSS cases are sporadic, and only a few patients have a maternally inherited form of the disease.

**PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA**

PEO is a clinically and genetically heterogeneous condition associated with single or multiple mtDNA deletions and sporadic, autosomal dominant or autosomal recessive inheritance. Classically, the first signs arise in adulthood, with a few cases arising in adolescence or in early adulthood. Ophthalmoplegia, prosis and muscle weakness with exercise intolerance are the main signs. Sensory motor neuropathy, sensorineural hearing loss, cataracts and cerebellar involvement are other progressive symptoms.

Cognitive deterioration with psychiatric manifestations may develop. Similar to KSS, single deletions/duplications in mtDNA are responsible for lactic acidosis, ragged red fibres and a mosaic pattern of defective cytochrome c oxidase on muscle histochemical investigations.

Autosomal dominant forms of PEO (adPEO) are mainly caused by mutations in four nuclear genes: POLG1, twinkle, DNA2 and ANT1. They are associated with ragged red fibres in skeletal muscle and multiple deletions of mtDNA. The typical clinical features of adPEO are progressive muscle weakness, most severely affecting the external eye muscles. Ataxia, depression, hypogonadism, hearing loss, peripheral neuropathy and cataracts are various other signs.

Other sporadic or recessively transmitted PEO cases can be linked with POLG mutations (Zeviani and Di Donato 2004).

**MYOCLONIC EPILEPSY WITH RAGGED RED FIBRES**

MERRF is a maternally inherited encephalomyopathy, characterised by myoclonus, cerebellar ataxia and mitochondrial myopathy. Seizures, hearing loss, dementia, peripheral neuropathy and multiple symmetric lipomas are frequently associated (Zeviani and Di Donato 2004).

In most cases, symptoms begin between the ages of 5 and 13 years with cerebellar ataxia, tremor and myoclonic jerks (see also Chapter 16) induced by action or intended movement. Many patients have generalised or massive myoclonic seizures and some become demented. Hearing loss, optic atrophy and proprioceptive sensory loss may occur. PEO, retinal degeneration or stroke-like episodes are not present. The severity of symptoms along a maternal lineage varies greatly from severe to mild manifestations, sometimes with only abnormal visual evoked response and EEG pattern. CSF and serum lactate levels may be slightly increased. Endocrine disorders may occur.

EEG records abnormal background activity, variously associated with spike–wave patterns and a photoparoxysmal response. Visual, auditory and somatosensory evoked response studies may show abnormal latencies, while EMG shows myopathic changes. CT and MRI may indicate cerebral and cerebellar atrophy. At post-mortem examination, degeneration of the cerebral hemispheres, cerebellar dentate nuclei, posterior spinal column and spinocerebellar tracts has been found.

COX-depleted ragged red fibres and ultrastructurally abnormal mitochondria in biopsed muscle are constant and may be the only sign in asymptomatic individuals within a family. The typical mitochondrial DNA mutation is in the tRNAlys gene A8344G. Other mutations in the same gene have been reported in association with MERRF, MERRF/ MELAS overlap syndrome and other complex phenotypes.

**MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS AND STROKE-LIKE EPISODES**

Mitochondrial myopathy, encephalopathy lactic acidosis and stroke-like episodes (MELAS) generally presents in children or young adults after normal early development. Symptoms include recurrent vomiting, migraine-like headache, and recurrent stroke-like episodes causing cortical blindness, hemiparesis or hemianopsia. Seizures are often preceded by strokes or episodes of migraine with aura and are invariably partial motor in type. Intellectual regression and behavioural problems are prominent. The myopathy is usually asymptomatic or expressed as muscular weakness and mild amyotrophy.
Additional features include short stature, diabetes mellitus, sensorineural hearing loss, mild retinal degeneration and cardiac involvement. Lactate levels in plasma and CSF are usually high, and creatine kinase can be increased. The CSF protein content is normal.

The EEG is usually abnormal, with occasional spike and wave or focal spike discharges. Neuroimaging shows focal lucencies or increased T2 signal, generally not in a vascular distribution, affecting various sites of the white matter, cortex or brainstem, and areas of calcification or high T2 signal in the basal ganglia. Cerebral and cerebellar atrophy may be associated. Focal necrosis and laminar cortical necrotic changes are the histopathological signs of the disease, together with neuronal degeneration and mineral deposits within the basal ganglia. The pathogenesis of the infarct-like lesions is presumably due to a mitochondrial micro-angiopathy with deficient energy metabolism in the endothelium of small pial arterioles and capillaries. Ragged red fibres, lipid droplets and abnormal mitochondria are present in muscles.

The most common mtDNA mutation is in A3243G, the tRNAleu (UUR) gene. However, many other mutations are associated with MELAS. Conversely, this A3243G mutation has been detected in patients with maternally inherited PEO or diabetes mellitus and deafness, and isolated myopathy or cardiomyopathy.

**ALPERS DISEASE**

Alpers–Huttenlocher syndrome (AHS), an autosomal recessive hepatocerebral syndrome of early onset, is a degenerative disease that primarily affects the cerebral grey matter. The typical course of AHS includes severe developmental delay, intractable seizures, cortical blindness, progressive liver dysfunction, acute liver failure after exposure to valproic acid and death in childhood. AHS is one clinical phenotype associated with a mitochondrial depletion syndrome due to POLG1 mutations resulting in mtDNA depletion and multiple respiratory chain defects in all affected tissues (Horvath et al. 2006). Seizures and EEG abnormalities are much more prominent than in Leigh syndrome, which is a reflection of the extensive involvement of cortical grey matter. Variable visceral involvement may be associated.

**MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY**

MNGIE is an autosomal recessive disease clinically defined by gastrointestinal dysmotility, cachexia, ptosis, ophthalmoplegia, peripheral neuropathy and white matter changes in brain MRI. This devastating disorder is linked to nuclear mutations in the thymidine phosphorylase gene. They induce pathological accumulation of thymidine and deoxyuridine, and imbalance of the mitochondrial pool impairing mtDNA replication and/or maintenance, with depletion, multiple deletions and point mutations (Nishino et al. 2001).

MNGIE usually manifests in late adolescence with gastrointestinal dysmotility characterised by dysphagia, gastroparesis and recurrent vomiting that lead to cachexia. Neurological impairments comprise ptosis and ophthalmoplegia, with late onset and progressive axonal and demyelinating sensorimotor polyneuropathy. Cognitive impairment is typically absent. Lactic acidosis is usually mild, and the protein level in CSF is increased in most patients. T2-weighted and fluid attenuated inversion recovery MRI brain sequences show large confluent hyperintense signal changes indicating leukoencephalopathy. They are mainly localised in the periventricular areas, and may affect the cerebral peduncles, brainstem and pons.

**PYRUVATE DEHYDROGENASE DEFICIENCY**

Pyruvate dehydrogenase complex (PDHc) deficiency is an important cause of encephalopathy associated with lactic acidosis. The clinical symptoms vary considerably, ranging from early lactic acidosis to intermittent ataxia, Leigh syndrome and progressive neurodegenerative disease with intellectual disability (Betendzen et al. 2006; Debray et al. 2006; De Meirleir et al. 2006) (see Fig 9.23).
Biochemical and Genetic Background

PDHC controls the entry of pyruvate, the glycolytic end-product, into mitochondria for oxidative metabolism and thus plays an important regulatory role in cellular energy metabolism in glycolytic-dependent organs such as the CNS. In the brain, PDHC is required for the formation of acetylcholine from acetyl-CoA. Thus, PDHC defects are expected to involve the nervous system.

PDHC is a mitochondrial multi-enzyme complex comprising three catalytic enzymes (E1, E2, E3), two regulatory enzymes (PDH kinase and phosphatase), and three coenzymes (thiamine, lipoic acid, FADH2). Additionally, an E3 binding protein (E3BP) probably has a structural function. The E1 component is a hetero-tetramer of two alpha- and beta subunits that share a thiamine pyrophosphate binding site. All components are encoded by nuclear genes located on the autosomes with the exception of the E1 alpha-subunit, which is located on chromosome Xp22.3.

The vast majority of patients have a defect in the E1 alpha-subunit with an X-linked transmission. More than 80 disease-causing mutations in the PDHA1 gene have been identified. Most of the mutations originate de novo, and in 25% of cases, the mother is a carrier. Males and females are equally affected with severely affected females not as common, depending on the X-inactivation pattern in different tissues, notably in the brain (Tulinius et al. 2005; Willemsen et al. 2006). There are more than 20 reported cases of E3 defect with a common mutation found particularly in Ashkenazi Jewish patients. About the same number of E3BP deficiency cases have been reported without prevalent mutations (Brown et al. 2006; Miné et al. 2006). Mutations in the genes for the defects in E1 alpha subunit, PDH phosphatase and E2 component have been identified in a few patients (Head et al. 2005).

Genetic counselling is possible and reliable antenatal diagnosis relies on molecular analyses in families whose molecular defect has been determined.

Clinical Features of PDH Deficiency

Male patients with PDHE1alpha deficiency can present with an overwhelming lactic acidosis in the neonatal period or in infancy. Hypotonia and apnoeic spells are the most frequent features. Most patients die within the first few months of life after a clinical course marked by failure to thrive, developmental delay, hypotonia, respiratory difficulties and seizures. In some patients, congenital brain malformations are present. Partial hypoplastic or thin corpus callosum, asymmetrical dilatation of ventricles and migrational defects are common. A second type of presentation, especially in males, includes Leigh syndrome (see previous sub-section). Symptoms occur after an apparently uneventful period of a few months. Seizures or episodes of weakness, respiratory failure, ataxia or dystonic posturing are the first manifestations. Later, these episodes may recur, and varying degrees of progressive neurological impairment and developmental delay are seen. Optic atrophy, ptosis, ophthalmoplegia and retinal degeneration have been mentioned.

In girls, atypical hypsarrhythmia or severe myoclonic seizures have been described. Facial dysmorphism suggesting fetal alcohol syndrome has been seen in patients with E1 deficiency. Many patients die within a few years but some survive with severe disability.

Finally, a small subset consists of patients who are clinically normal or have mild developmental delay and who experience intermittent neurological episodes of recurrent ataxia, acute dystonia, extrapyramidal movement disorders or muscle weakness with myopathy and/or peripheral neuropathy (Tulinius et al. 2005; Debray et al. 2006; Willemsen et al. 2006).

PDHE1alpha defects are the most frequent abnormality within these last two groups. However, the rare reported cases of PDHE2, PDHE3 and PDH phosphatase deficiencies can be associated with these clinical forms. E3BP deficiency may present in the neonatal period with lactic acidosis. However, most have survived well into childhood or even adulthood with variable impairment (Brown et al. 2006).

In neonatal-onset forms, MRI studies have shown severe abnormalities including agenesis or dysgenesis of the corpus callosum, heterotopias and pachygria, asymmetrical ventriculomegaly, periventricular and subependymal cysts, and hypomyelination. In late-onset forms, progressive lesions in the basal ganglia and brainstem are common. A high peak of lactate on brain MRS is an indicative sign. Neuropathological findings confirm brain dysgenesis. Dysplasia and ectopia of the inferior olivary nuclei, dysplasia of the dentate nuclei, absence or hypoplasia of the medullary pyramids, periventricular neuronal heterotopias and deficient myelination are other findings (Head et al. 2005).

Biochemical Features

The most important laboratory tests for diagnosis are the measurement of lactate and pyruvate in blood and CSF. Both are usually elevated with a low to normal lactate to pyruvate ratio. These can be severe during the neonatal period or during episodes of deterioration. Definite diagnosis is made by assay of PDHc activity and molecular investigations.

Treatment of PDH Deficiency

Thiamine has been beneficial in a few patients. Dichloroacetate inhibits PDH kinase and is effective in lowering plasma lactate levels, although clinical improvement is not obvious (Berendzen et al. 2006; Stacpoole et al. 2006). By providing alternative energy fuel, the ketogenic diet is probably the most effective therapeutic approach.

Pyruvate Carboxylase Deficiency

This is a rare autosomal recessive disorder presenting with lactic acidosis and neurological involvement.
**Biochemical Background**

Pyruvate carboxylase is a biotin-containing enzyme that catalyses the first step of gluconeogenesis by converting pyruvate to oxaloacetate. Pyruvate carboxylase also plays an anaplerotic role mainly in the brain and muscle by replenishing the tricarboxylic cycle. Pyruvate carboxylase is an astrocytic-specific enzyme that allows neurotransmitter synthesis by supplying glutamine, and is a key factor for myelin synthesis by providing citrate (Brun et al. 1999). Pyruvate carboxylase activity is expressed in fibroblasts with various residual enzymatic activities without frank correlation with clinical phenotypes. The most severe form (French or B phenotype) is associated with the absence of apoprotein on Western blot analysis, while in the milder form (North American or A phenotype) a detectable apoprotein is present. Various mutations in the pyruvate carboxylase gene have been found in both A and B phenotypes. Prenatal diagnosis is possible by measurement of pyruvate carboxylase activity in cultured amniocytes or in fresh chorionic villus samples, or by DNA analyses.

**Clinical Features of Pyruvate Carboxylase Deficiency**

Three different clinical presentations are described according to the severity of clinical and biochemical manifestations (García-Cazorla et al. 2006). The French phenotype is a neonatal-onset form with an overwhelming lactic acidosis. Patients present within the first hours of life with acute and relentless neurological deterioration and metabolic ketoacidosis. They have hypokinetic lethargy, axial hypotonia, large-amplitude tremors, seizures, and abnormal ocular movements such as nystagmus.

Some patients have hepatic failure with persistent cytolyis and/or cholestasis. In addition, they may suffer a severe renal tubular acidosis with loss of bicarbonate. Death in the first few months of age is the rule.

Patients with the North American phenotype have a later onset with a progressive developmental delay, pyramidal signs, ataxia and nystagmus. In addition, they suffer intermittent metabolic ketoacidosis exacerbated by intercurrent infections. They have a longer survival. A third benign form has been described in rare patients with nearly normal development and who display intercurrent ketoacidosis that improves with symptomatic treatment.

The biochemical pattern in neonatal forms is notable for the presence of a secondary hyperammonaemia with citrullinaemia, and a very high lactate/pyruvate ratio contrasting with a low beta-hydroxybutyrate/acetoacetate ratio. In CSF, lactate, lactate/pyruvate ratio, and alanine are increased and glutamine is decreased.

On neuroimaging, the most specific changes are ischaemic-like lesions with a diffuse white matter abnormality and periventricular cysts that are almost invariably haemorrhagic. Subdural, intraventricular and intracerebellar haemorrhages have also been reported. A similar description reported in two cases during the last trimester of pregnancy (Brun et al. 1999) underlines the prenatal severity and the irreversibility of brain involvement. In milder forms, leukodystrophy is the main sign. No basal ganglia lesions have been reported. CNS pathology has shown poor myelination involving cerebral and cerebellar white matter and sometimes the base of the pons, loss of neurons in the cerebral cortex, ventricular enlargement, thinning of the corpus callosum and proliferation of astrocytes.

**Treatment**

Therapeutic trials have attempted to replenish the Krebs cycle using glutamate, aspartate, citrate and odd-numbered fatty acid (triheptanoine) supplementation, but all have failed to prevent neurological deterioration (Mochel et al. 2005; García-Cazorla et al. 2006).

**Defects in Krebs cycle**

Defects in the Krebs cycle include dihydrolipoamide dehydrogenase deficiency, fumarase and alpha-ketoglutarate dehydrogenase deficiency.

**Dihydrolipoamide dehydrogenase deficiency**

Dihydrolipoamide dehydrogenase deficiency (DLD) is a component of a number of mitochondrial multienzymes, including pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase and branched-chain alpha-ketoacid dehydrogenase (Cameron et al. 2006). The clinical phenotype of DLD deficiency may range from a severe neonatal disorder to less severe presentations in childhood. In infancy, patients present with intermittent ketoacidosis, neurological signs, microcephaly and Leigh syndrome resulting in intellectual disability, ataxia, and hypotonia. A less severe form in childhood is characterised by episodic vomiting, ketoacidosis, liver dysfunction, hypotonia, and exercise intolerance between episodes in a few patients. Biologically, periods of decomposition are marked by hyperlactataemia accompanied by increased urinary excretion of alpha-ketoglutaric acid and, less constantly, by increased levels of branched-chain amino acids in plasma. Brain imaging investigations reveal various patterns from nonspecific periventricular white matter lesions to signs of Leigh syndrome with involvement of the basal ganglia. Mutations in the DLD gene have been reported, with a common mutation (229G>C in exon 9) in patients with Ashkenazi Jewish ancestry.

**Fumarase deficiency**

Fumarase deficiency has been reported in a few children with severe neurological impairment (Kerrigan et al. 2000). The clinical phenotype is characterised in infancy by severe
developmental delay with hypotonia, seizures, facial dysmorphism, growth failure, relative macrocephaly, and death in the first years of life. Hyperlactacidaemia can be mild, but urinary excretion of fumaric acid is diagnostic. On brain MRI, lesions can be severe with ventriculomegaly, polymicrogyria, agenesis of the corpus callosum, decreased white matter volume and relative hypoplasia of the brainstem. Autopsy in a case has revealed hypomyelination and heterotopia located in cerebellum, occipital and parietal areas. The defect involves both cytosol and mitochondrial isoforms and appears to be autosomal recessive (Deschauer et al. 2006).

### ALPHA-KETOGLUTARATE DEFICIENCY

Alpha-ketoglutarate deficiency has been described in a few neonates and infants (Bonnefont et al. 1992). The clinical presentation resembles that of early-onset PDH deficiency or the mitochondrial encephalomyopathies. Mild hyperlactacidaemia is associated with abnormal alpha-keto-glutaric acid in urine with or without increased excretion of other Krebs cycle intermediates. All patients had cortical atrophy but with striatal necrosis in some cases.

### MITOCHONDRIAL FATTY ACID BETA-OXIDATION DEFECTS

Inborn errors in mitochondrial fatty acid oxidation represent a group of disorders that affect energy metabolism during fasting and metabolic stress. As a consequence, common features include acute metabolic decompensations associated with fasting, recurrent hypoglycaemia, Reye-like syndrome and unexplained sudden infant death. Chronic involvement of fatty-acid-dependent tissues may result in myopathy, cardiomyopathy, seizures and intellectual disability. More than 25 different defects are known (Longo et al. 2006; Tein et al. 2013).

### BIOCHEMICAL BACKGROUND OF MITOCHONDRIAL FATTY ACID OXIDATION

The general pathway of mitochondrial fatty acid oxidation and the sites of the different known enzymatic defects are shown in Figure 9.26. Long-chain fatty acids converted to their CoA esters are first converted into long-chain acylcarnitines by carnitine palmitoyltransferase I (CPT-I) on the inner side of the outer mitochondrial membrane and are transported into the mitochondria by a carnitine acylcarnitine translocase (CACT).
and are then converted back to their CoA esters by CPT-II on the inside of the inner mitochondrial membrane. Medium and short-chain fatty acids readily diffuse into the mitochondrial matrix where they are then activated into their CoA esters for ensuant intramitochondrial beta-oxidation. Primary carnitine deficiency, CPT-I, CPT-II and translocase deficiencies impair mitochondrial transport of long-chain fatty acids and consequently beta-oxidation and ketogenesis. Intramitochondrial beta-oxidation involves four sequential steps with chain-length-specific enzymes. The first step requires four distinct acyl-CoA dehydrogenases, the very long-(VLCAD), long- (LCAD), medium- (MCAD) and short-chain acyl-CoA dehydrogenases (SCAD) which transform fatty acyl-CoA to enoyl-CoA. All four acyl-CoA dehydrogenases release electrons that pass to the respiratory chain via the electron transfer flavo-protein system. The latter specific electron transfer system is shared with other flavoprotein dehydrogenases: glutaryl-CoA- and isovaleryl-CoA-dehydrogenases. The three remaining steps of beta-oxidation can be performed by either a single trifunctional protein (TFP) for long-chain substrates, or by three chain-length-specific enzymes for short-, medium- or long-chain substrates. Each four-step beta-oxidation cycle releases acetyl-CoA, which enters the Krebs cycle in tissues such as heart and muscle. In liver, during the fasting state, acetyl-CoA is converted to ketones (ketogenesis), which are exported to peripheral organs, such as the brain, for final oxidation (ketolysis) and energy delivery.

Multiple acyl-CoA dehydrogenase (MAD) deficiency, called glutaric aciduria type II, is caused by a defect in the electron transfer system. Several alternative pathways become important when mitochondrial beta-oxidation is impaired. Omega-oxidation in microsomes and peroxisomes results in the production of characteristic dicarboxylic acids, and intramitochondrial conjugation of acyl-CoA to glycine and carnitine is an important mechanism of detoxification.

The biochemical diagnosis is based on the identification of abnormal dicarboxylic acids and their by-products (glycine, carnitine) in urine. Glutaric and branched-chain organic acidurias are associated in MAD deficiency. It should be emphasised that these specific patterns are best detected during an acute crisis, whereas in the homeostatic state the most reliable tests are the determination of total and esterified plasma carnitine levels and the identification of abnormal acylcarnitine profiles in plasma or dried blood spots.

Measurement of fatty acid oxidation rates in fresh lymphocytes or cultured skin fibroblasts is a useful tool to narrow the search for the specific defect involved. Direct enzymatic assay may then be performed for definitive diagnosis. Most defects are expressed in cultured fibroblasts; however, certain of these defects, such as muscle CPT-I and SCHAD deficiencies, may be tissue-specific (Sim et al. 2002).

Genetic Background
Overall, these disorders are frequent, but MCAD and CPT-II deficiencies are the most common. All the disorders that have been identified are inherited as autosomal recessive traits. Heterozygotes are usually normal. However, mothers with heterozygous long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) carrying an affected fetus may develop acute fatty liver of pregnancy in the third trimester. All the implicated genes have been cloned, and various disease-causing mutations have been described. Prevalent mutations are associated with MCAD, adolescent–adult form of CPT-II deficiency, and alpha and beta subunit of TFP deficiency. Antenatal diagnosis is available by measuring the enzymatic activity in cultured amniocytes or in chorionic villus samples, and more reliably, by molecular analysis. The high prevalence of these disorders associated with the availability of effective treatments and/or preventive measures make them good candidates for expanded newborn neonatal screening, which has been implemented in a number of countries, particularly for MCAD deficiency (Wilcken et al. 2003).

Clinical Findings in Fatty Acid Oxidation Defects
Patients affected with fatty acid oxidation defects have in common certain clinical presentations that are related to acute energy deprivation that may occur at any age from the neonatal period to adulthood. However, neonates, infants and young children are the most susceptible to decompensations during metabolic stress due to their limited glucose reserves. At birth, the affected neonates are unable to cope with the energy demand. In infants and young children, prolonged fasting and intercurrent infections are the most frequent precipitating factors. In older children, infections, fever and prolonged exercise may induce decompensations.

Clinically, these acutely ill patients may manifest life-threatening episodes of hypoketotic hypoglycaemia, cardiomyopathy and arrhythmia, coma and multi-organ failure. Hepatic encephalopathy with lactic acidosis and hyperammonaemia may mimic Reye syndrome and these children are at risk for recurrent ‘Reye-like’ episodes. Various degrees of rhabdomyolysis and/or cardiomyopathy are frequently associated, particularly in the long-chain fatty acid oxidation (FAO) disorders. In some cases, rapid unexpected death may suggest sudden infant death syndrome (SIDS). In most situations, this abrupt deterioration is associated with hypoketotic hypoglycaemia, lactic acidosis, hyperammonaemia, signs of liver failure, and muscular involvement with increased creatine kinase. Despite correction of blood glucose levels, some patients may display persistent lethargy, seizures, or opisthotonus due to concomitant cerebral oedema which suggests that elevated levels of fatty acid intermediates are neurotoxic. The mortality rate is high, particularly in the neonatal period. In survivors, many patients appear asymptomatic between episodes. Others display chronic involvement of muscle and heart, or suffer neurological sequelae with seizures and developmental delay. These neurological sequelae have been observed with MCAD deficiency, a disorder that is otherwise considered as the mildest fatty oxidation defect.

CPT II deficiency has three distinct clinical entities: an adult, infantile, and a perinatal form, all with an autosomal recessive inheritance pattern.
The adult CPT-II clinical phenotype is more benign and requires additional external triggers such as high-intensity exercise before the predominantly myopathic symptoms are elicited. The perinatal and infantile forms involve multiple organ systems. The perinatal disease is the most severe form and is invariably fatal. The introduction of mass spectrometry to analyse blood acylcarnitine profiles has revolutionised the diagnosis of fatty acid oxidation disorders including CPT-II deficiency. Its use in expanded neonatal screening programmes has made presymptomatic diagnosis a reality. An increasing number of mutations are being identified in the CPT-II gene with a distinct genotype–phenotype correlation in most cases.

**Specific features of fatty acid oxidation defects**

In neonates, beyond the acute presentation, abnormal organogenesis with dysmorphic features has been described. Cystic dysplasia of the brain and kidneys and polymicrogyria are encountered in some MAD and severe neonatal CPT-II-deficient patients (North et al. 1995). In SCAD deficiency, primary neurological signs such as hypotonia, hyperactivity, and developmental delay suggest severe impairment of cerebral maturation, potentially due to specific neurotoxicity of short-chain fatty acid metabolites (Tein 2002).

Recurrent episodes of rhabdomyolysis during mild to moderate prolonged exercise and proximal muscle weakness resulting from insufficient ATP production are characteristic signs of fatty acid oxidation defects, particularly of the long-chain fatty acid oxidation disorders. Chronic muscle weakness with lipid storage myopathy has been described in all these defects with the exception of liver-CPT-I deficiency. Muscular weakness associated with a progressive hypertrophic and/or dilated cardiomyopathy is a characteristic feature of primary systemic carnitine deficiency due to OCTN2 deficiency that most often presents in infancy. Later onset in adulthood associated with cardiac arrhythmia has been described. The mild form of MAD in adolescence and adulthood may present with progressive muscular weakness and exercise intolerance. The diagnosis is of importance since certain patients are clearly riboflavin-responsive.

Acute episodes of rhabdomyolysis are frequent and serious complications of defective long-chain fatty oxidation, i.e. CPT-II, VLCAD, LCHAD, TFP, and MAD deficiencies, but have also been seen in M/SCHAD deficiency. The most common cause of recurrent rhabdomyolysis in both male and female children is the mild adolescent–adult form of CPT-II deficiency. It is characterised by episodes of rhabdomyolysis without other organ involvement and without muscular weakness or creatine phosphokinase elevation between acute episodes. These episodes are triggered by prolonged exercise, fasting, intercurrent infections or cold exposure. Investigation for a fatty acid oxidation defect and particularly for CPT-II deficiency should be included in the diagnostic work-up of all patients presenting with recurrent myoglobinuria particularly if triggered by FAO stressors and should also be considered following a first attack of rhabdomyolysis if there are no obvious exogenous factors (e.g. toxins, trauma, vascular compromise, inflammation, etc.). The recurrent episodes of rhabdomyolysis may contribute to the ongoing muscle weakness in patients with trifunctional protein or VLCAD deficiency, who may also develop progressive axonal neuropathy and pigmentary retinopathy (den Boer et al. 2003; Spiekerkoetter et al. 2004; Tyni et al. 2004).

**Treatment in fatty acid oxidation defects**

The mainstay of therapy is the prevention of fasting and catabolic states, avoidance of mild to moderate prolonged exercise and cold exposure (shivering thermogenesis) and the prompt treatment of infection and fever. In acute situations, intravenous glucose infusion (8–10mg/kg/min) should be started without delay. There is no clear evidence that restricting dietary fat is useful in MCAD deficiency. In contrast, in patients with defects of long-chain fatty acid metabolism, a high carbohydrate, low-fat frequent feeding diet supplemented with medium-chain triglycerides may be beneficial. Essential fatty acids (EFA) should also be supplemented during a fat-restricted diet to prevent EFA deficiency. In patients with primary systemic carnitine (OCTN2) deficiency, lifelong high-dose oral carnitine supplementation (100–300mg/kg/day) is life saving and reverses the cardiomyopathy and myopathy within a few months. Some patients with mild variants of MAD and SCAD deficiencies may respond to riboflavin supplementation. Docosahexaenoic acid supplementation may improve/ameliorate the neuropathy and retinopathy in patients with LCHAD/TFP. Prevention of muscular pain and exercise intolerance by pre-exercise supplementation with oral corn-starch (provided there is not excessive weight gain) or medium-chain triglycerides may be beneficial (Gillingham et al. 2006; Ogier de Baulny and Superti-Furga 2006).

### Defects of cholesterol metabolism

#### Mevalonic aciduria

Mevalonic aciduria is an inborn error of cholesterol biosynthesis due to mevalonate kinase deficiency. This defect is associated with two clinical entities: hyper-IgD and periodic fever (HIDS), and classic mevalonic aciduria. HIDS is characterised by recurrent febrile crises that usually start in the first year of life without apparent neurological abnormalities. Conversely, mevalonic aciduria is typically characterised by developmental delay, ataxia and dysmorphic features. Patients also experience acute episodes of fever.
The febrile seizures are often associated with hepatosplenomegaly, lymphadenopathy, abdominal symptoms, arthralgia and skin rashes. Presently, both disorders are considered to represent a unique disease with a clinical and biochemical continuum (Simon et al. 2004; Waterham and Clayton 2016).

**Biochemical Background and Pathogenesis**

Mevalonate kinase (MVK), which phosphorylates mevalonic acid, is a central enzyme in the isoprenoid pathway with cholesterol, dolichol and ubiquinone as major end products, rendering this pathway crucial for cell proliferation and cellular function (Fig. 9.27). The respective pathogenic roles of end-product shortage and toxicity of mevalonate accumulation are unclear. Either appears sufficient to explain multi-organ involvement and the teratogenic aspects of the disorder suggested by the high rate of miscarriages and stillbirths of malformed fetuses in affected families.

Postnatally, cerebellum and retina seem to be very susceptible to oxidative stress and/or to the toxicity of mevalonic acid. The mechanism of the autoinflammatory process remains unclear.

**Genetic Background**

Mevalonic aciduria and HIDS are autosomal recessive disorders with about 180 disease-causing mutations identified in the MVK gene. Some mutations are preferentially linked to the HIDS phenotype and three others are relatively common. Most patients are compound heterozygotes for two different mutations whose combined effect on residual enzymatic activity may account partially for phenotypic variability. Mevalonate kinase activity is expressed in fibroblasts, leukocytes, amniotic cells and chorionic villi. Prenatal diagnosis has been performed by assaying chorionic villus samples for enzymatic activity and amniotic fluid for mevalonic acid. More reliably, it can be performed by molecular testing in the gene for MVK (Waterham and Clayton 2016).

**Clinical Features**

The disorder may manifest from infancy to childhood with marked phenotypic heterogeneity. Severe forms may be lethal in early infancy or even lead to intrauterine death. Conversely, mild forms may survive infancy and lead to various disabilities. Mevalonic aciduria and HIDS have in common recurrent...
autoinflammatory episodes that last 3–5 days. They may recur as often as twice a month in infancy and tend to be less frequent later in childhood. They are marked by high fever, abdominal pain, vomiting and diarrhoea, lymphadenopathies, hepatosplenomegaly and skin rashes. In addition, patients affected with mevalonic aciduria have psychomotor retardation of varying degree. Most patients over 2 years develop progressive ataxia, dysarthria and progressive cerebellar atrophy. Muscle hypotonia with weakness is present in all patients. Reduced growth velocity, anaemia, permanent hepatosplenomegaly and lymphadenopathy are common. Mild dysmorphism was present in 8 of 11 cases reported by Hoffmann et al. (1993). Cataracts, uveitis, progressive retinal dystrophy and optic atrophy lead to progressive visual impairment. Partial or generalised tonic–clonic seizures have been described in a few patients. Less severely affected patients may survive until adolescence and even adulthood with mild disability and many fewer acute episodes of fever (Simon et al. 2004).

**Biochemical Diagnosis**

The diagnosis relies on organic acid analysis to identify mevalonic acid accumulation in body fluids. Mevalonic aciduria is usually elevated in the classic phenotype but may not be diagnostic in less severe forms. Permanent hyper-IgD and/or IgA is observed in HIDS, while in the mevalonic aciduria phenotype, it is inconstant. The best diagnostic tools are measurement of enzyme activity in leukocytes or fibroblasts, and the molecular investigation.

**Treatment**

No effective therapy is available. Supplementation with presumably deficient end products such as cholesterol, bile acids and ubiquinone has not produced any clinical or biochemical improvement. Blocking mevalonate hyperproduction by low doses of HMG-CoA reductase inhibitor (lovastatin) has resulted in severe crises in two patients with mevalonic aciduria. The best therapeutic approach seems to be intermittent corticosteroid therapy.

**Other Disorders of Cholesterol Metabolism**

**Smith–Lemli–Opitz Syndrome**

This syndrome results from a defect in the biosynthesis of cholesterol due to a block at the level of the enzyme 3-beta hydroxysterol D-7 reductase (Waterham 2006). It is an autosomal recessive disease with intellectual disability and with severe automutilation. Typical dysmorphic findings are microcephaly, short upturned nose, often cleft palate or uvula, short stature, postaxial polydactyly and 2–3 toe syndactyly. Cardiac and genital defects are also common. Severe photosensitivity can be present. A clue to the diagnosis can be a low cholesterol and increase of 7-dehydrocholesterol and confirmed by genetic analysis in the DHCR7 gene.

Treatment with cholesterol supplementation and HMG-CoA reductase inhibition has shown some benefit on the failure to thrive and seems to have some effect on neuromotor development (Svoboda et al. 2012).

Other rare malformation syndromes due to defects in the biosynthesis of cholesterol include CHILD disease (congenital hemidysplasia with ichthyosiform erythroderma and limb defects), Conradi–Hünermann syndrome (X-linked dominant chondrodysplasia punctata) and desmosterolosis (Haas et al. 2001) (see Fig 9.25).

**Niemann–Pick Disease Type C**

**Biochemical and Genetic Background**

Niemann–Pick disease type C (NPC) is a neurovisceral and degenerative disorder of autosomal recessive inheritance. The estimated prevalence of NPC is 1:150,000. Biochemically, it is characterised by abnormal intracellular trafficking of endocytosed LDL-cholesterol resulting in accumulation of unesterified cholesterol in the endosomal/lysosomal system and impairment of the retrocontrolled reactions. In addition, partial inhibition of sphingomyelinase by free cholesterol is responsible for mild sphingolipid storage. In NPC fibroblasts, accumulation of free cholesterol is demonstrated by filipin staining, and study of LDL-induced cholesterol ester formation. Both tests serve the biological diagnosis and differentiate between classic and variant phenotypes (Vanier et al. 1991). Genetically, the disorder is due to mutations in two different genes that encode for two proteins functioning in tandem or in sequence in this metabolic pathway (Blom et al. 2003; Vanier and Millat 2003; Sleat et al. 2004). Approximately 95% of patients have mutations in the NPC1 gene (mapped at 18q11), which encodes a large membrane glycoprotein with late endosomal localisation. The remainder have mutations in the NPC2 gene (mapped at 14q24.3), encoding a small soluble lysosomal protein (Verot et al. 2007). More than 200 disease-causing mutations are described in the NPC1 gene as well as many polymorphisms. Reliable prenatal diagnosis uses molecular investigations on chorionic DNA when familial mutations have been clearly defined.

**Clinical Features of Niemann–Pick Type C**

In the neonatal period, NPC is mainly a visceral disease with hydrops fetalis, prolonged jaundice, or severe interstitial pneumonia, especially in patients with NPC2. A cholestatic icterus with hepatomegaly may be present in half the cases during the neonatal period. A few of these patients develop severe hepatic failure, leading to death before the appearance of neurological symptoms. Survivors have persistent hepatosplenomegaly, while jaundice spontaneously disappears before the age of 3 months. The onset of neurological problems can occur at any time over years or even decades in this group of patients.
Neurologically, patients are classified based on the age at onset, which is an indicator of prognosis despite some overlap between groups (Imrie et al. 2007; Vanier 2010).

In severe cases, patients present in infancy. They have hepatosplenomegaly, hypotonia and delayed motor development before 2 years of age. Deterioration is rapid, mainly marked by loss of acquired skills, spasticity, and atomic episodes of a cataplectic nature but without epilepsy. Many of these patients die before 5 years of age without having developed ophthalmoplegia.

In late infantile forms, the onset is usually in early school years. The affected children suffer increasing physical and intellectual disability. Poor school progress and unsteady gait are usually the first neurological manifestations. Hepato and/or splenomegaly are often associated signs. Progressive additional features are cataplectic episodes seizures, vertical supranuclear ophthalmoplegia and swallowing difficulties. Many patients become wheechair-dependent and incapable of continuing in school. Death occurs during the second decade of life in about 50% of cases. Death before 10 years of age and survival beyond the second decade are not unusual.

In the juvenile form (6–15 years), the onset of neurological signs is more insidious. Learning difficulties are the main initial signs and may be isolated for years before another neurological sign such as cerebellar ataxia, vertical gaze palsy (especially marked in downward movements) or psychiatric problems, lead to the diagnosis. Visceromegaly is not a prominent sign at this age. However, a neonatal history of prolonged icterus, present in about half the cases, could be a leading retrospective sign. Cataplexy and seizures develop in about 20% of patients. The course of the disease is further marked by disabling cerebellar ataxia, dystarthria, dysphagia and dementia. Other striking manifestations are psychiatric disturbances, dystonia, movement disorder and grimacing. Death usually occurs within the second decade.

In adults, the symptomatology is insidious, and patients mainly present with either prominent psychiatric signs or predominant movement and gait impairment (Klarner et al. 2007; Sévin et al. 2007; Sedel 2016).

Neuroimaging is generally not contributive towards diagnosis. Foamy histiocytes found in bone marrow aspirate stain with filipin. The definitive diagnosis requires cultured fibroblasts to perform the filipin staining test and the functional analysis of cholesterol esterification. Nowadays, confirmation of diagnosis is performed by mutational analysis.

No specific treatment is available. Cataplexy can be improved by clomipramine or modafinil. Inhibition of glycolipid synthesis by miglustat has been studied in a number of patients and can improve or stabilise the neurological features (Sedel 2016).

**Wolman Disease and Cholesterol Ester Storage Disease**

Wolman disease and cholesterol ester storage disease (CESD) are two phenotypic expressions of lysosomal acid lipase (LAL) deficiency, which results in massive accumulation of cholesteryl esters and triglycerides in most tissues. Wolman disease represents the early-onset form, which is uniformly fatal, while CESD is a more benign type with later onset (Assmann and Seedorf 1995). Both disorders are autosomal recessive. Structural mutations of the LAL gene, which has been localised to chromosome 10 (10q23.2–23.3), have already been identified without clear genotype-phenotype correlation (Muntoni et al. 1995).

Prenatal diagnosis is available by assaying LAL activity in amniotic cells or chorionic villus samples.

Clinical features include severe diarrhoea, hepatomegaly and failure to thrive. Hypotonia and intellectual disability become apparent after initially normal development. In Wolman disease, massive calcification of the adrenals is characteristic. Hepatomegaly, increased transaminases, progressive liver fibrosis and cirrhosis can be seen in children and adults (Burton et al. 2015).

Diagnosis is based on the demonstration of LAL deficiency in cultured fibroblasts, lymphocytes or other tissues. Hyperlipoproteinaemia is common in CESD but absent in Wolman disease.

Recently ERT with Sebelipase alfa was developed and studies resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with LAL deficiency.

**DISORDERS OF COPPER METABOLISM**

**WILSON DISEASE**

**HEPATOLENTICULAR DEGENERATION**

**Pathology and pathophysiology**

Wilson disease is an autosomal recessive disorder, affecting especially the basal ganglia, associated with cirrhosis of the liver (Fig. 9.28; see also Chapter 19). The disease is due to a defect in the hepatic excretion of copper into bile that results in accumulation of copper, starting in the liver then in other tissues, especially in the brain. The primary defect is absence or dysfunction of the hepatic ATPase due to over 300 currently known mutations in the ATP7B gene.

Normally, 20–50% of ingested copper is absorbed from the intestine and transported as an albumin complex to the liver. In the liver, the copper is incorporated into newly synthesised ceruloplasmin for transport to the rest of the body, excretion into the biliary system, or incorporation into copper storage proteins such as metallothione. More than 95% of serum copper is normally in the form of ceruloplasmin. The normal concentration of ceruloplasmin in the plasma of children
older than 2 years is 200–430 µmol/L (30–65 mg/dL). Low levels are frequent in infants and younger children and are of no diagnostic value. Plasma level is elevated during pregnancy, with high oestrogen concentration, liver cirrhosis, malignant disease and hyperthyroidism. Ninety-five per cent of patients with Wilson disease have markedly diminished ceruloplasmin levels. However, this is not a constant finding and ceruloplasmin levels as low as those in Wilson disease (e.g. in nephrosis patients) may not be associated with symptoms. The same applies to familial ceruloplasmin deficiency, in which clinical manifestations include blepharospasm and retinal degeneration. This rare disease is associated with iron storage in CSF and is due to a deficit of a copper ferroxidase essential for iron equilibrium (Xu et al. 2004).

The basic defect is liver accumulation of free copper, due to deficient ceruloplasmin, that acts as a toxic substance. The basic molecular defect is absence or reduced function of a protein that has copper-transporting ATPase activity and a marked amino acid homology with the copper transport protein that is mutated in Menkes kinky hair disease (Tanzi et al. 1993). This impedes transport of copper from hepatocytes to bile and results in accumulation of copper. The gene coding for this protein maps to 13q14.3, and a large number of mutations are known (Thomas et al. 1995). Most patients appear to be compound heterozygotes for different mutations, and the genotype seems to affect clinical findings, particularly the age at onset (Houwen et al. 1995).

Accumulation of copper initially damages hepatocyte mitochondria and peroxisomes. Eventually, excess copper leaks from the liver into blood and is taken up by tissues. In the brain, the basal ganglia are particularly affected with secondary damage.

Pathologically, the liver shows focal necrosis with secondary postnecrotic cirrhosis. Copper is initially diffusely spread within the cytoplasm and secondarily becomes sequestered within lysosomes. In the brain, the basal ganglia show spongy degeneration, loss of neurons and large numbers of large protoplasmic astrocytes (Alzheimer type II glia). The frontal lobe cortex is similarly involved. Copper is present in the cornea and is deposited in clumps close to the endothelial surface of Descemet’s membrane, which is responsible for the Kayser–Fleischer ring.

**Clinical features of Wilson disease**

Wilson disease is transmitted as an autosomal recessive trait with a frequency of 1 in 100,000 in homozygous form. In about one-third of cases, the disorder presents at 3–5 years of age with hepatic manifestations. Of all patients, 30% present with neurological symptoms, usually after eight years of age. In about 10% of children, Wilson disease first presents as an acute or intermittent haemolytic anaemia (Prella et al. 2001); the remainder may show a mixture of hepatic and cerebral changes. Psychiatric symptoms are frequent (Oder et al. 1991), sometimes so predominant as to constitute a psychiatric form of the disorder.

Neurological manifestations usually begin from 10 years of age onwards, except that, in some populations, rare patients may have neurological symptoms as early as 3 years. All types of movement disorder can be seen including tremor and myoclonus. Facial grimacing is a classic feature. Four major clinical types are recognised: the dystonic form, the ‘pseudosclerotic’ type, a parkinsonian–rigid form (Oder et al. 1991), and a choreic form.

Most cases of the neurological form with onset before adulthood are of the dystonic type with facio-linguo-pharyngeal involvement causing facial masking, dysarthria and dysphagia, associated with or preceded by intellectual deterioration or psychiatric problems (Medalia et al. 1988). Speech is often severely impaired. Choreic and myoclonic movements are frequently...
observed, and painful spasms are common. Pyramidal signs are infrequent. The course may be acute, but, in most cases, it is slowly progressive. During the late stages, muscular rigidity is generalised, bizarre dyskinetias often appear and the patients are severely incapacitated. Psychiatric manifestations are often prominent with severe psychotic or depressive symptoms. The pseudocerebrotic form of Wilson disease is rare in adolescents, but intermediate types are not uncommon. In such cases, dysarthria, intention tremor and asterixis are prominent.

Hypokinesia and rigidity, sometimes with tremor at rest are features of the rigid–akinetic type. In many cases, several different syndromes coexist or occur in succession. In a few cases, tongue dyskinesia or tongue tremor with dysarthria are the sole manifestations.

Almost all patients with neurological features have a Kayser–Fleischer ring that may be seen with the naked eye or require slit lamp examination. It may be complete or incomplete and may be present even in the presence of normal liver function.

**Diagnosis of Wilson Disease**

The diagnosis of Wilson disease rests on a high index of suspicion. Wilson disease must be thought of first in any child or adolescent with dystonia and an extrapyramidal syndrome, and in those with psychotic and behavioural disorders, because this is a treatable disease. The Kayser–Fleischer ring is an essential clue.

In about half the cases, neuroimaging shows symmetrical areas of hypodensity in the thalamus and basal ganglia (Fig. 9.25) that are visible both with CT and MRI (Roh et al. 1994) as low T1 and high T2 signals. Such abnormalities may decrease or disappear with chelating treatment.

Urinary copper is high (in excess of 0.8 µmol/day), as is non-ceruloplasmin-bound copper. Serum ceruloplasmin level is generally higher than 13–17 µmol/L (100 mg/L), and serum copper is higher than 9 µmol/L (50 mg/dl; normal value 14–30 µmol/L, 90–160 mg/dl). Increased urinary excretion of copper (greater than 100 micrograms per 24 hrs), especially after challenge with D-penicillamine 500 mg and a repeated dose after 12 hours, is usually conclusive.

Prenatal diagnosis and detection of presymptomatic cases is possible with molecular techniques demonstrating mutations in the ATP7B gene (Tümer et al. 1994).

**Treatment Treatment in Wilson Disease**

Initial therapy needs to eliminate excess copper in symptomatic patients and patients then need lifelong maintenance therapy to reduce copper level and prevent reaccumulation of copper. Various agents are used. They include chelators of copper, including D-penicillamine, triethylenetetramine (trientine) and tetrathiomolybdate. Chelators are used to produce a negative copper balance and decrease the copper load.

The first effective chelating treatment was D-penicillamine (15–25 mg/kg/day; 0.5–0.75 mg/day for children under 10 years, 1 mg/day in older patients), given orally in divided doses. Pyridoxine 25 mg/kg/day is added because of the antivitamin effect of penicillamine.

Treatment should be started progressively and the dosage should be slowly increased. Side effects are frequent and may be severe in up to a quarter of cases. They include lupus erythematosus, nephrotic syndrome, fever, rashes, pyridoxine deficiency, thrombocytopenia and, rarely, myasthenic symptoms.

Triethylene tetramine (trientine) at a dose of 40–50 mg/kg/day seems to be very efficacious; it is well tolerated and is regarded as the first-choice drug by some authorities (Brewer et al. 2006). Its association with zinc seems particularly effective. It is clearly indicated when penicillamine is poorly tolerated or as initial treatment in moderate or severe forms of the disorder. However, it may also produce transient aggravation.

Treatment with chelators must be closely monitored clinically and by watching copper excretion, which often increases dramatically upon starting treatment then returns to normal over a few months. When effective, the Kayser–Fleischer rings begin to fade in a few weeks and should disappear completely in about a year.

Oral zinc sulphate treatment, at a dosage of 300–600 mg/day (Hoogenraad 2006), is meant to decrease toxic free copper by binding it to metallothioneine, decreasing gut absorption of copper and rendering it non-toxic. It is often used as a complement to chelators and is also effective alone as shown by normalisation or decrease of free blood copper and disappearance of Kayser–Fleischer rings. Some investigators consider it to be the first-choice treatment (Hoogenraad 2006). Others prefer to use it together with trientine for moderate or severe forms and advise zinc for mild neurological cases or non-neurological presentations (Brewer et al. 2006). Zinc has been used successfully for presymptomatic children with subclinical liver involvement as indicated by high levels of transaminases. Gastrointestinal intolerance may occur. It does not produce iatrogenic paroxysmal intoxication. A low copper diet is recommended in all cases.

Most children who have isolated hepatic disease usually do well on treatment. Approximately 40–50% of those with neurological manifestations become asymptomatic. Patients with advanced liver disease or acute liver failure can benefit from liver transplantation, which is often practised in refractory disease (Dhawan et al. 2005).

Zinc therapy is important in young presymptomatic patients, pregnant patients, and as a maintenance after de-coppering treatment.

**Menkes Disease**

(Kinky Hair Disease, Steely Hair Disease, Trichopoliodystrophy)

Menkes disease is an uncommon, X-linked disease (incidence 1 in 50,000 births) characterised pathologically by multiple
focal involvement of the brain grey matter and by low serum copper and ceruloplasmin. Figures 9.29 and 9.30 the gene (MKN) is located at Xq13.3 and codes for a copper-transporting ATPase (ATPase7A). Deficiency of this protein results in lack of transport of copper to cellular organelles. There is a secondary deficit of several copper-dependent enzymes including cytochrome c oxidase and lysine oxidase, accounting for bone and connective tissue abnormalities. The expression of the disease can be extremely diverse even with the same mutation (Borm et al. 2004). Many mutations have been identified: in particular splicing mutations resulting in an incomplete gene with partial activity responsible for allelic variants, especially the occipital horn syndrome (Qi and Byers 1998).

**Pathology and Pathophysiology**

Copper levels are low in the liver and brain but are elevated in intestinal mucosa and kidneys. Orally administered copper is poorly absorbed but intravenous copper produces a brisk rise of serum copper. The copper content of fibroblasts is markedly elevated. This suggests maldistribution of copper that becomes unavailable for the synthesis of copper-containing enzymes. DNA analysis can permit first trimester diagnosis if the mutation in the family has been identified (Tümer et al. 1994).

Defective activity of metalloenzymes produces diffuse disturbances that particularly affect arteries in the brain and elsewhere, and cause extensive focal degeneration of the grey matter with neuronal loss and gliosis. There is profound involvement of the cerebellar cortex (Robain et al. 1988) with loss of Purkinje cells. Remaining cells show abnormal dendritic and axonal swellings.

**Clinical Manifestations of Menkes Disease**

Clinical manifestations may be present from the neonatal period or after 2–3 months. Failure to thrive is the most striking feature. Seizures soon occur that can include infantile spasms (Bahi-Buisson et al. 2006; Bindu et al. 2007), and a profound deterioration with hypotonia becomes apparent. Hypothermia is an important clue although commonly unrecognised. The hair is sparse, brittle, and grey or silvery. Microscopic examination easily confirms the diagnosis by showing pili torti and occasionally trichorrhexis nodosa. The cherubic appearance of affected infants is striking. In the first few weeks of life the primary hair may be normal; however, even neonatal hair may have a special appearance (Gu et al. 2005). The skin is very loose.

Hydroureters and hydronephrosis are common. Generalised osteoporosis, metaphyseal spurring, diaphyseal periosteal reaction, scalloping of the posterior aspect of the vertebral bodies and multiple wormian bones are often present. Angiography shows elongated and tortuous arteries but is not routinely indicated. However, tortuosity of intracranial arteries is well demonstrated by imaging and aneurysms may develop. Neuroimaging techniques show diffuse brain atrophy, defective myelination and often subdural haematomas. In some cases, more focal abnormalities with areas of cortical atrophy and associated hypodensity are seen (Takahashi et al. 1993). The course is rapidly downhill and the mean age at death is 19 months.

Early diagnosis may be difficult to make firmly as low copper levels may occur normally in the neonatal period and this may delay the diagnosis, which is highly regrettable as copper-histidine therapy should be started early. A low urine homo-vanillic/vanillylmandelic acid ratio due to the
decreased activity of the copper-dependent enzyme dopamine beta-hydroxylase may be suggestive (Matsuo et al. 2005). Prenatal diagnosis can be done by genetic analysis (Gu et al. 2002).

Other early clues are a low birthweight and preterm birth, which are present in a third of cases, and the unusual colouration of the hair.

**Variants of kinky hair disease**

Milder cases of the condition are known and may present with ataxia and mild intellectual disability (Kodama et al. 1999) and run a less malignant course. Other atypical cases have presented with hypotonia and hair anomalies but without seizures or hypothermia (Inagaki et al. 1988). The occipital horn syndrome features hyperelastic and bruiseable skin, hyperextensible joints and calcification at the junction of the neck muscles and occipital bones (Qi and Byers 1998). Abnormalities in copper metabolism are similar to those of Menkes disease, but less marked (Proud et al. 1996). There may be intellectual disability.

**Treatment of menkes disease**

Administration of copper-histidine, either by subcutaneous or intramuscular injection, not only corrects copper levels but results in clinical improvement, particularly if started as early as 35 weeks gestational age (Tümer et al. 1996) and not later than 10 days post-term. Munakata et al. (2005) have shown that the treatment improves some of the biochemical disturbances (increased lactate and decreased N-acetyl aspartic acid as shown by proton MRS). However, evaluation of results is still difficult. After the treatment is started, after the neonatal period, histidine copper has no more effect due to the blood–brain barrier and seizures will increase. Improvement with copper-histidine is also dependent on the mutation, some genotypes having a partial copper transport capacity.

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**DISORDERS OF PURINE AND PYRIMIDINE METABOLISM**

**PURINES**

Purines are essential building-stones for nucleic acids, but are also components of other important biological molecules such as ATP, GTP, cAMP, NADH and Acetyl-COA. The purine source is exogenous (meat) and endogenous de novo synthesis. This biosynthesis is in several steps. They are catabolised to uric acid and then excreted through the kidneys. The purines are synthesised through several steps and then degraded and excreted as uric acid.

There are three disorders in purine synthesis that lead to well characterised neurological disease; a few others are less well described and more rare.

**LESCH–NYHAN DISEASE**

**Pathophysiology**

Lesch–Nyhan disease is an X-linked deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT catalyses the conversion of hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP), an important salvage pathway for the synthesis of purines. As a consequence of this enzymatic defect, hypoxanthine and guanine cannot be converted to the corresponding nucleotides IMP and GMP. Hypoxanthine is then catabolised to xanthine and uric acid and excreted. The increased
production of uric acid and the depletion of hypoxanthine, which acts as a feedback regulator of uric acid synthesis, leads to a markedly increased concentration of uric acid in all body fluids, hyperuricaemia and hyperuricosuria and its consequences (urate lithiasis and gout). The mechanism of the neurological disease manifestations is still obscure and is unrelated to uric acid. They may result, at least in part, from a mixture of abnormal neurodevelopment and neurotransmitter abnormalities (Hyland et al. 2004). Failure of development of dopaminergic synaptic terminals has been demonstrated. The concentration of dopamine and the activity of enzymes involved in its synthesis are lessened, and this and other alterations in neurotransmitter balance within the basal ganglia are probably important.

There is a striking degree of genetic heterogeneity of HGPRT defects. Over 300 pathogenic mutations in the HGPRT gene located at Xq26–q27 are known (Jinnah et al. 2004), and the spectrum of severity is extremely wide (Puig et al. 2001). This can range from asymptomatic cases to the most severe classic syndrome, depending on the degree of residual enzyme activity and probably also other yet unknown modulating factors.

Genotype–phenotype studies indicate no clear relationship to specific mutations (Jinnah et al. 2004); however, mutations that produce a null enzyme are typically associated with the most severe phenotype.

**CLINICAL MANIFESTATIONS OF LESCH–NYHAN DISEASE**

The clinical manifestations are striking. They become apparent during the first year of life in the form of developmental delay and generalised hypotonia or dystonia. Patients are usually mistakenly diagnosed with quadriplegic or dystonic cerebral palsy. Abnormal movements usually appear between 6 months to 1 year of age. Dystonia is constant; choreoathetosis or ballismus are subsequently superimposed in 44–90% of patients (Jinnah et al. 2006) but are not progressive after the first few years (see also Chapter 19). Some degree of spasticity develops progressively. Ocular saccades are sometimes initiated by head movements or eye blinking, reflecting involvement of the basal ganglia. Seizures are uncommon but bouts of dystonic opisthotonus can occur and may resemble seizures.

Self-mutilation is the most striking feature and one that raises major problems. The most common behaviour is biting of the fingers, lips and tongue that appears usually between 2 and 4 years of age but sometimes later. This behaviour often results in severe lesions of the mouth or hands that are difficult to prevent. Head banging, extension of the arms while being wheeled through doorways or putting fingers in the wheel spokes, and eye poking come next in frequency (Robey et al. 2003). Affected children are variably intellectually disabled, usually mildly or moderately with global IQ scores between 60 and 70, but most suffer from attention deficit and difficulties of comprehension of complex or lengthy speech and in multistep reasoning. They are severely disturbed by their compulsion to self-mutilate and appear happier when maintained in restraints.

In late childhood or adolescence, haematuria, renal calculi and ultimately renal failure develop. Gouty arthritis can also be observed.

**DIAGNOSIS AND TREATMENT OF LESCH–NYHAN DISEASE**

The diagnosis is suggested by elevated serum uric acid levels. However, determination of the ratio of uric acid to creatinine in a morning sample of urine is a better screening test. Enzymatic analysis of HGPRT in erythrocytes or fibroblasts confirms the diagnosis, followed by gene analysis. Asymptomatic carrier mothers can be identified.

Treatment with allopurinol is effective in relieving the symptoms due to high uric acid but has no impact on the neurological manifestations. Attempts at gene therapy are being pursued. Treatment of the neurological problem is mainly with behaviour modifiers and neurotransmitter therapy. Gabapentin has been reported to be efficacious in one patient. Deep brain stimulation has been tried with variable success.

**PARTIAL DEFICITS IN HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE AND VARIANTS OF LESCH–NYHAN DISEASE**

Deficits in HGPRT less complete than those in the classic Lesch–Nyhan disease (<1.3% of normal activity) can produce various clinical pictures. Patients with an enzymatic activity level of more than 8.5% of normal have no neurological symptoms but may have uric acid-related problems. At intermediate range, a neurological picture similar to Lesch–Nyhan syndrome but without intellectual disability and self-mutilation may be observed (Puig et al. 2001). Other variants with mild intellectual disability, spasticity and skeletal malformations, choreoathetosis, developmental delay and deafness have been described. Although intelligence is normal in most cases, comparison of patients with partial HGPRT deficiency with normal individuals has shown intermediate levels between those of controls and those with the classic syndrome.

**ADENOSYLSUCCINATE LYASE DEFICIENCY**

Jaeken and van den Berghe (1984) were the first to report on an autism syndrome with intellectual disability in association with the presence of large amounts of succinyladenosine (S-AMP) and succinylaminomimidazole carboxamide riboside (SAICAR) in the CSF and urine.
Pathophysiology

Adenosylsuccinate lyase (ADSL) catalyses two steps in the synthesis of purine nucleotides. This leads to conversion of SAICAR into AICAR and the conversion of S-AMP into AMP. When ADSL is deficient SAICAR and S-AMP accumulate.

Clinical features

Most patients have been classified as type 1, combining psychomotor delay and autistic features, followed by epilepsy in childhood. Later, patients with neonatal intractable encephalopathy were described and even an earlier presentation is intrauterine growth impairment, microcephaly, fetal hypokinesia and absent fetal heart rate variability (Moucheh et al. 2007). In type 2 patients intellectual disability is less pronounced with a picture of autism, a behaviour resembling Angelman syndrome (Gitiaux et al. 2009 see also Chapter 5) or associated with seizures.

This disorder should be thought of in infants with early-onset seizures and in children with autism spectrum disorder.

Genetics

ADSL (gene ADSL on 22q) deficiency is an autosomal recessive disorder. There is a common mutation R426H in type 1 and R303C in milder cases.

Diagnosis

This can be confirmed by the presence of succinylpurines in the CSF (SAICAR, S-Ado). Many gene mutations are known.

Treatment

Therapeutic trials have been performed with D-ribose and uridine, however results were not convincing (Jurecka et al. 2008).

Disorders of Pyrimidine Degradation

Defects of dihydro pyrimidine dehydrogenase (DPD) (van Gennip et al. 1994) and of dihydropyrimidine dehydrogenase (DHP) (Putman et al. 1997) have been reported to be associated with convulsions, intellectual disability or choreoathetosis, and sometimes dysmorphism.

Dihydropyrimidine dehydrogenase deficiency

Clinical features of dihydropyrimidine dehydrogenase deficiency (DPD) can be found in children with epilepsy and psychomotor delay, associated with hypertonia, growth delay, microcephaly and autistic features (van Gennip 1997). The second presentation is in adults who receive 5-fluorouracil, used in cancer treatment and resulting, in these patients, in highly enhanced toxicity with neutropenia, stomatitis, gastrointestinal perforations and neurological deterioration.

There is an increase of excretion of uracil. The diagnosis can be confirmed enzymatically or by gene sequencing. The infantile form is inherited as an autosomal recessive form; the adult form is seen in heterozygotes.

Dihydropyrimidinase deficiency

Dihydropyrimidase deficiency (DHP) (Assmann et al. 1997, Kuilenburg 2010) leads to severe developmental delay, epilepsy, dysmorphic features or microcephaly. Some have no symptoms at all. Some patients also have cyclic vomiting, reflux or malabsorption.

Urinary dihydrouracil and dihydrothymine are elevated. The enzyme assay requires a liver biopsy. Mutation analysis of the DPYS gene is possible.

Beta-ureidopropionase deficiency

Beta-ureidopropionase (also called Beta-alanine synthase) deficiency, can result in severe dystonia, intellectual disability and a severe defect in myelination, cerebellar hypoplasia but is also seen in asymptomatic infants (Assmann et al. 2006).

There is an elevation of ureidopropionic acid and ureidoisobutyric acid in the urine.

Disorders of Creatine Synthesis and Transport

Creatine and phosphocreatine (PCr) are major components in energy storage and transmission. Creatine is mainly synthesised in the liver and the pancreas in a two-step mechanism from glycine, arginine and methionine and finally converted by non-enzymatic cyclisation to creatinine (Fig. 9.31). Humans maintain their creatine pool by biosynthesis and nutritional uptake of 1–2 g/day. Creatine is transported via the blood and at the cellular level by the Cr-transporter system (CrT).

Three diseases have been described in this pathway: arginine glycine amidinotransferase deficiency (AGAT), guanidino acetate methyl transferase deficiency (GAMT) and creatine transporter deficiency (CrT). They lead to absence of creatine and phosphocreatine in the brain.

Developmental delay, severe speech disturbances, intellectual disability and autistic behaviour are common, and usually recognised between 6–12 months and more clearly between 2–3 years of age.
Figure 9.31  Pathways of creatine synthesis and transport.

GUANIDINOACETATE METHYLTRANSFERASE DEFICIENCY

CLINICAL FEATURES
The first patient with guanidinoacetate methyltransferase (GAMT) deficiency was reported by Stöckler et al. (1994). The child was normal at birth but became hypotonic, and developed extrapyramidal dystonic symptoms and severe psychomotor retardation. MRI at 12 months of age showed abnormal signals in the globus pallidus. Proton MRS revealed the absence of brain creatine and creatine phosphate signals, suggesting an inborn error of creatine synthesis. Deficient GAMT activity was confirmed in liver tissue.

Most patients have the severe phenotype with an extrapyramidal movement disorder and drug-resistant epilepsy. The onset of the seizures associated with a developmental regression usually occurs in the second and third year. Seizures include myoclonic, generalised tonic–clonic, partial complex seizures and drop-attacks (Mercimek-Mahmutoglu et al. 2006). Most children have no active speech. On MRI, there is delayed myelination and/or bilateral hyperintensity in the globus pallidus (Schulze 2003).

DIAGNOSIS
Pathognomonic laboratory findings in GAMT-deficiency consist of decreased concentrations of creatine and creatinine in blood, CSF and urine, while guanidinoacetate, the precursor of creatine, is elevated in the same fluids. The absence of a creatine PCr signal in brain MRS is almost diagnostic. Further biochemical and genetic studies allow the identification of the underlying defect.

GAMT-deficiency is an inherited autosomal disease; the gene maps to chromosome 19p13.3. Several mutations have been identified.

TREATMENT
Early treatment can be important. Creatine monohydrate 300–400mg/kg per day in total, given in 3–6 doses (Stickeler-Ipsiroglu et al. 2006) resulted in an improvement of the extrapyramidal signs and better control of the seizures.

Further guanidinoacetate (GAA) reduction by giving 800mg ornitine per kg per day in 3–6 doses and dietary arginine restriction requiring 0.4–0.7g natural protein per kg and a synthetic arginine-free mixture with essential amino acids gave some further improvement. A further reduction of GAA precursors can be obtained by adding sodium benzoate (100mg/kg/day) (Stockler-Ipsiroglu et al. 2006).

ARGININE GLYCINE AMIDINOTRANSFERASE DEFICIENCY

AGAT deficiency deficiency was first described in 2001 (Item et al. 2001).

CLINICAL FEATURES
Very few patients have been described. Most symptoms such as developmental delay, delayed speech and mild to moderate intellectual disability are nonspecific. No seizures have been reported.
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D I A G N O S I S

Creatine in serum is normal, GAA slightly decreased and the excretion of GAA in urine extremely low. The enzymatic diagnosis of AGAT-deficiency can be made in fibroblasts and lymphoblasts and confirmed by gene sequencing (GATM) on chromosome 15q15.3.

T R E A T M E N T

Treatment consists of creatine monohydrate 400mg/kg/day in total given in 3–6 doses (Stockler-Ipsioglu 2006), again with good results if treatment is started early.

X-LINKED CREATINE TRANSPORTER DEFICIENCY

Several families have been described since the first patient in 2001 (Salomons 2001) (Fig. 9.32).

C L I N I C A L FEATURES

This disorder features mild intellectual disability and severe delay in the expression of speech and language function in boys. Apart from mild hypotonia, motor functions are normal.

Focal seizures, failure to thrive and behavioural abnormalities can be part of the clinical picture (Degrauw et al. 2002). The speech disorder is an expressive aphasia. Behaviour abnormalities have been described as aggressive with autistic features. Seizures are usually mild and infrequent (Fons et al. 2009). A variety of other organ manifestations such as megacolon, chronic constipation and gastrointestinal ulcers have been described. Females can have a mild cognitive delay and learning difficulties.

D I A G N O S I S

Creatine concentrations in plasma and urine are elevated, while GAA is normal. The urinary creatine to creatinine ratio is increased, but can be normal in females. MRI is normal and MRS reveals reduced or almost complete absence of the creatine signal (Fig. 9.32). Mutations are found in the X-linked creatine transporter SLC6A8 gene mapping to Xq28 (Salomons et al. 2003).

T R E A T M E N T

There is not an efficient treatment (Stockler-Ipsioglu 2006). Adding L-arginine 400mg/kg/day and L-glycine 150mg/kg/day is still inconsistent in success. Seizures can usually be controlled with valproate or carbamazepine.

CEREBROTENDINOUS XANTHOMATOSIS

Cerebrotendinous xanthomatosis (CTX) is a rare inherited disorder of bile acid metabolism leading to the accumulation of cholestanol and cholesterol in most tissues including the CNS. It is responsible for xanthomas, early cataract, severe neurological deterioration and premature atherosclerosis. In spite of its rarity, a diagnosis is important because early treatment can halt and, in some, cases reverse the neurological impairment (Federico and Dotti 2003).
Cholestatic jaundice in infancy might be the first manifestation (Clayton 2002). This improves but subsequent symptoms appear: intellectual disability in the first decade and cataaracts as early as 5 years. In the second decade, additional neurological signs appear with spastic paraparesis, peripheral neuropathy, ataxia and dysphasia. Psychiatric symptoms mimicking schizophrenia also occur (Berginer et al. 1988).

Tendon xanthomata can develop, from the second decade on. Premature coronary heart disease or atherosclerosis have been reported. Xanthomas may be absent in the early stages of the disorder or even never develop, and a few patients have had normal intelligence in spite of neurological impairment such as ataxia, paresis or peripheral neuropathy (Björkhem et al. 1987). In the late and final stage, neurological deterioration is severe, speech becomes difficult, and swallowing difficulties and sphincter incontinence develop. MRI studies of the brain and spinal cord have demonstrated cerebral, cerebellar and spinal cord atrophy (Bencze et al. 1990) and demyelination in the cerebrum, cerebellum and spinal cord (Arpa et al. 1995). The defect impairs the mitochondrial part of bile acid synthesis from cholesterol and results in the accumulation of cholesterol and cholesterol. The definitive diagnosis relies on the measurement of 7-alpha-hydroxylase in cultured fibroblasts.

Cerebrotendinous xanthomatosis is an autosomal recessive disorder resulting from a mutation of the CYP27A1 gene affecting the 27-hydroxylase mitochondrial enzyme activity.

Supplementation of the end-product of bile acid synthesis, chenodeoxycholic acid, decreases cholesterol accumulation and results in a clinical, radiological and neurophysiological improvement (Björkhem et al. 1987). Addition of simvastatin, an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase, may further improve the therapeutic effects.

Results of neurophysiological studies are consistent with a demyelinating or mixed axonal and demyelinating peripheral neuropathy (Arpa et al. 1995). The biochemical diagnosis is made by the determination of excessive urinary excretion of bile alcohols and by the measurement of cholesterol/cholesterol ratio in serum (Björkhem et al. 1987; Arpa et al. 1995). The defect impairs the mitochondrial part of bile acid synthesis from cholesterol and results in the accumulation of cholesterol and cholesterol. The definitive diagnosis relies on the measurement of 7-alpha-hydroxylase in cultured fibroblasts.

**HYPOTONIA–CYSTINURIA SYNDROME**

This syndrome resembles the Prader-Willi syndrome (PWS) clinically and is characterised by generalised severe hypotonia at birth, nephrolithiasis due to cystinuria, growth hormone deficiency, some facial dysmorphia and failure to thrive. Later, patients develop hyperphagia and rapid weight gain.

Cystinuria is found in by urinary amino acid analysis.

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- Metachromatic Leukodystrophy Due to Saposin B Deficiency
- Multiple Sulphatase Deficiency
- Globoid Cell Leukodystrophy
  - Krabbe Disease
- X-Linked Adrenoleukodystrophy
  - Addison Disease and Cerebral Sclerosis, Melanodermic Leukodystrophy;
  - Siemerling-Creutzfeldt Disease, Bronzed Schilder Disease
- Other Peroxisomal Disorders
  - Alexander Disease
  - Giant Axonal Neuropathy
  - Canavan Disease
    - Canavan-Van Bogaert-Bertrand Disease; Spongy Degeneration of CNS;
    - Aspartoacylase Deficiency
- Leukoencephalopathy with Vanishing White Matter
  - Vanishing White Matter Disease, Vanishing White Matter Leukodystrophy,
    - Childhood Ataxia with CNS Hypomyelination, Myelinopathy Centralis Diffusa
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  - Vacuolating Megalencephalic Leukoencephalopathy with Subcortical Cysts;
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Heredodegenerative Disorders

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A significant proportion of genetically transmitted neurological diseases have not yet been linked with demonstrated metabolic errors, especially known enzymatic deficits. Many are characterised by early degeneration of one or more specific central nervous system (CNS) areas or systems. Some demonstrate morphological evidence of storage at the microscopic or ultramicroscopic level. A majority show only ‘degenerative’ lesions of the brain and in some cases of the peripheral nervous system. These disorders are caused by genetic abnormalities of structural or enzyme proteins. Many of these have been identified in the recent past; some of them are yet to be identified. These disorders are termed heredodegenerative CNS disorders. They share most of the clinical features of recognised metabolic diseases; in particular, they are progressive illnesses. A symptom-free interval and a loss of previously acquired skills are frequent but not constant features, especially in cases with congenital or early infantile onset when the progressive nature may be difficult to determine. This group is highly heterogeneous, including many disorders with no real link between them. The various conditions studied in this chapter will be grouped mainly according to gross pathological criteria; for example, on the system or part of the CNS that bears the brunt of the disease, although topographic delimitation is far from being always precise. Pathological location is relatively well correlated with the clinical features.

Heredodegenerative disorders can have their onset at any age, and age at onset is an important diagnostic clue. Because no specific biological disturbance is known for several of these conditions, their diagnosis rests on clinical grounds, especially careful history taking, family investigation and neurological examination, and on certain laboratory tests – radiological, neurophysiological, ophthalmological or biochemical. Brain biopsy that was used for the diagnosis of some heredodegenerative CNS disorders has been largely replaced, over the past two decades, by biopsies of peripheral tissues.

Study of this group of disorders has been revolutionised by the progress of molecular genetics and the use of linkage techniques. These permit identification of mutations within or close to the relevant gene or in the proteins they code, making reliable diagnosis possible. When the gene has been mapped and cloned, appropriate methods can be applied to help determine the abnormal gene product and, hopefully, understand the mechanisms of the disease and eventually prepare possible therapies. DNA studies may permit prenatal diagnosis, and, in some cases, preimplantation procedures. With direct study of the gene sequence, mutations or deletions can be detected, enabling precise determination of the genotype and consequently of the subtype and genetic origin of the disorder. Diagnosis by molecular genetic techniques has medical and ethical implications which have to be carefully considered. There is no doubt though that molecular genetic techniques have opened exciting new perspectives in the field of heredodegenerative diseases.

For convenience, a few diseases that are not progressive but have similar clinical presentations and are also of genetic origin will be included in this discussion.

LEUKODYSTROPHIES

The leukodystrophies comprise a group of genetic diseases that affect the white matter of the brain and, in a few disorders, also peripheral myelin. There is no classification available that covers all aspects of clinical presentation, morphological alterations, or metabolic and genetic characteristics. In a broad sense leukodystrophies are defined as genetic white matter brain disorders. They belong to a larger group of conditions that affect predominantly the white matter, termed leukencephalopathies, which also include other hereditary disorders as well as acquired disorders involving the white matter. The leukencephalopathies produce imaging features that can closely resemble those of the leukodystrophies proper and constitute a major differential diagnosis (Table 10.1).

Originally the classification of leukodystrophies was based on morphological characteristics; examples are globoid cell leukodystrophy (Krabbe disease), metachromatic leukodystrophy and sudanophilic leukodystrophy. This last term has more or less disappeared as a result of advances in understanding of the genetic aetiology of most leukodystrophies. The terms demyelination, dysmyelination and hypomyelination describe the possible pathophysiological aspects. Demyelination refers to the breakdown of structurally and biochemically normal
myelin (e.g. in multiple sclerosis); dysmyelination denotes a structurally and biochemically abnormal or unstable myelin (e.g. adrenoleukodystrophy); while hypomyelination indicates disturbance and delay in the formation of myelin (e.g. adrenoleukodystrophy); while hypomyelination indicates disturbance and delay in the formation of myelin (e.g. in multiple sclerosis); dysmyelination denotes a structurally and biochemically abnormal or unstable myelin (e.g. adrenoleukodystrophy); while hypomyelination indicates disturbance and delay in the formation of myelin (e.g. in multiple sclerosis). Dysfunction of grey matter is increasingly recognised as a feature in many early-onset types. The classification of leukodystrophies as defined (Table 10.2) is primarily based on disturbances of cell organelles (lysosomes, peroxisomes, mitochondria), structural elements (neurofilaments) and metabolic processes. Table 10.3 classifies the leukodystrophies according to the genetic defect. Leukodystrophies with an identified genetic cause may be inherited in an autosomal dominant manner, an autosomal recessive manner, or an X-linked recessive manner. Genetic counselling regarding risk to family members depends on accurate diagnosis, determination of the mode of inheritance and identification of the responsible mutation. Prenatal testing for pregnancies at risk is possible if the responsible mutation is known.

From the clinical point of view, the leukodystrophies are characterised clinically by the predominance of motor involvement, especially pyramidal and cerebellar signs, with some degree of cognitive deterioration and low incidence of seizures, myoclonus and paroxysmal electroencephalogram (EEG) abnormalities. From the imaging point of view, all share involvement of white matter, best demonstrated by magnetic resonance imaging (MRI). Hyperintensity in the white matter in T2-weighted sequences is the MRI finding required for diagnosis of a leukodystrophy. T1-weighted sequences show hypointensity in the white matter in the demyelinating leukodystrophies and iso- or hyperintensity in the hypomyelinating leukodystrophies. The MRI findings, especially the type and distribution of the white matter involvement and the eventual presence of associated features (e.g. cysts, calcification, grey matter involvement, brainstem involvement, spinal cord involvement), together with the age at onset and the clinical findings, are the most valuable information to suspect a specific leukodystrophy and to orientate the diagnostic procedure especially the performance of specific biochemical or molecular genetic testing (see Table 10.3). For practical purposes, in the present chapter we will use this classification to separate the demyelinating/dysmyelinating and hypomyelinating leukodystrophies. The MRI features of white matter diseases have been reviewed by van der Knaap and Valk (2005) and more recently by Schiﬀmann and van der Knaap (2009), and magnetic resonance spectroscopic anomalies by Hanefeld et al. (2004).

<table>
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<th><strong>Table 10.1</strong> Disorders involving the white matter of the cerebral hemispheres and which may cause abnormal density or signal on imaging</th>
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<td>Fukuyama-type dystrophy</td>
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<td>Laminin alpha 2 deficiency</td>
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<td>Diffuse vascular disorders (CADASIL)</td>
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<td><strong>Acquired disorders</strong></td>
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<td>Diffuse post-anoxic encephalopathy</td>
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<tr>
<td>Periventricular leukomalacia (extensive forms)</td>
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<tr>
<td>Toxic leukoencephalopathy</td>
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<tr>
<td>(e.g. methotrexate, X-ray therapy, immunosuppressive agents)</td>
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<tr>
<td>Viral infections, e.g. acute encephalomyelitis, rare cases of subacute panencephalitis, congenital infections (TORCH)</td>
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<td>Transependymal resorption of CSF in some cases of hydrocephalus</td>
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</table>

*Adults only.*

DEMELINATING/DYSMYELINATING LEUKODYSTROPHIES

**METACHROMATIC LEUKODYSTROPHY**

Metachromatic leukodystrophy (MLD; MIM #250100) was first described by Scholz (1925) and Greenfield (1933). Scholz reported the genetic origin of the disease and separated it from disorders described under the term of diffuse sclerosis. The typical staining properties, showing metachromasia after staining with cresyl violet or toluidine blue in an acid solution, separate the disease from the so-called orthochromatic
Table 10.2 Classification of hereditary white matter disorders according to the organelles/structural elements/metabolic processes affected

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<tr>
<td>Multiple sulphatase deficiency (MSD)</td>
<td>Disorders of neurofilaments</td>
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<tr>
<td>Globoid cell leukodystrophy (GLD, Krabbe disease)</td>
<td>Alexander disease</td>
</tr>
<tr>
<td>Free sialic acid storage disease</td>
<td>Giant axonal neuropathy 1 (GAN1)</td>
</tr>
<tr>
<td>(Salla disease, infantile sialic storage disease)</td>
<td>Disorders of DNA repair</td>
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<td>Fucosidosis</td>
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MLD is an autosomal recessive disorder with an estimated prevalence of one in 40,000. It is caused by a deficiency of the lysosomal enzyme arylsulphatase A (ARSA). The deficiency of ARSA results in a storage of cerebroside sulphate (sulphatide). The genetic defect is localised on chromosome 22 (Polten et al. 1991). The accumulation of sulphatides leads to break down of central and peripheral myelin. Sulphatide concentration in affected tissue is increased and cerebroside concentration is decreased.

Besides the ARSA-alleles (frequency 0.5%) causing the late infantile, juvenile and adult-onset forms of MLD, another ARSA allele (frequency 7–15%) exists, which has been called ARSA pseudodeficiency (ARSA-PD) (Gieselmann et al. 1991). Ten to 20 per cent of individuals homozygous for this allele have a low ARSA activity but show no clinical symptoms and no sulphatiduria. Homozygosity for ARSA-PD is frequent in the general population; patients with neurological symptoms of other causes and ARSA-PD may therefore be misdiagnosed as having MLD. The pseudodeficiency allele

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<tr>
<td>Metachromatic leukodystrophy (MLD)</td>
<td>Arylsulphatase A (ARSA) deficiency</td>
<td>#250100</td>
<td>Autosomal recessive</td>
<td>ARSA (22q13.33)</td>
<td>Confluent dysmyelination with periventricular and frontal predominance, sparing of U-fibres, brainstem involvement, cerebellum involvement possible</td>
<td>Peripheral nervous system (PNS) involvement + see description of clinical features in main text</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy due to saposin B deficiency</td>
<td>Saposin B deficiency, cerebroside sulphatase activator deficiency</td>
<td>#249900</td>
<td>Autosomal recessive</td>
<td>PSAP (10q22.1)</td>
<td>Similar to MLD</td>
<td>Juvenile or more rarely late infantile phenotype of MLD</td>
</tr>
<tr>
<td>Multiple sulphatase deficiency (MSD)</td>
<td>Mucosulfatidosis, juvenile sulfatidosis type Austin</td>
<td>#272200</td>
<td>Autosomal recessive</td>
<td>SUMF1 (3p26.1)</td>
<td>Similar to MLD</td>
<td>Combines features of a mucopolysaccharidosis (coarse facial features, visceromegaly, skeletal abnormalities) with those of MLD</td>
</tr>
<tr>
<td>Globoid cell leukodystrophy (GLD)</td>
<td>Krabbe disease, galactosylceramide beta-galactosidase deficiency, galactocerebrosidase (GALC) deficiency</td>
<td>#245200</td>
<td>Autosomal recessive</td>
<td>GALC (14q31.3)</td>
<td>Confluent dysmyelination with periventricular and parieto-occipital predominance, cerebellum and brainstem involvement</td>
<td>Extreme irritability with sound-induced startle, spasticity, seizures, rapid progression, PNS involvement</td>
</tr>
<tr>
<td>X-linked adrenoleukodystrophy (X-ALD)</td>
<td>Addison disease and cerebral sclerosis, melanodermic leukodystrophy, Siemerling-Creutzfeldt disease, Bronzed Schilder disease</td>
<td>#300100</td>
<td>X-linked recessive</td>
<td>ABCD1 (Xq28)</td>
<td>Confluent dysmyelination with periventricular and parieto-occipital predominance with contrast enhancement, U-fibres spared, brainstem and cerebellum involvement possible, medullar involvement in adult myeloneuropathy</td>
<td>X-linked adrenal insufficiency + see description of clinical features in main text</td>
</tr>
<tr>
<td>Other peroxisomal disorders</td>
<td>See Table 10.4</td>
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</tr>
<tr>
<td>Alexander disease</td>
<td></td>
<td>#203450</td>
<td>95% sporadic, due to de novo heterozygous mutations, 5% autosomal dominant</td>
<td>GFAP (17q21.31)</td>
<td>Confluent dysmyelination with frontal predominance with white matter rarefaction and cysts and contrast enhancement, non-calciiefying lesions in basal ganglia, cerebellum, brainstem and spinal involvement possible</td>
<td>Macrocephaly in infantile type, bulbar symptoms in older patients + see description of clinical features in main text</td>
</tr>
<tr>
<td>Giant axonal neuropathy 1 (GAN1)</td>
<td>Autosomal recessive giant axonal neuropathy</td>
<td>#256850</td>
<td>Autosomal recessive</td>
<td>GAN (16q23.2)</td>
<td>Cerebellum involvement</td>
<td>Curly hair, PNS involvement</td>
</tr>
</tbody>
</table>

Continued
### Table 10.3  Classification of the demyelinating/dysmyelinating and hypomyelinating leukodystrophies according to genetic defects (continued)

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<td><strong>Name</strong></td>
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<tr>
<td>Canavan disease</td>
<td>Canavan-Van Bogaert-Bertrand disease, Spongy degeneration of central nervous system, aspartocylase deficiency</td>
</tr>
<tr>
<td>Leukoencephalopathy with vanishing white matter (VWM)</td>
<td>Vanishing white matter disease, Vanishing white matter leukodystrophy, Childhood ataxia with central nervous system hypomyelination, Myelinopathy centralis diffusa</td>
</tr>
<tr>
<td>Megalencephalic leukoencephalopathy with subcortical cysts 1 (MLC1)</td>
<td>Vacuolating megalencephalic leukoencephalopathy with subcortical cysts, Leukoencephalopathy with swelling and cysts, van der Knaap disease</td>
</tr>
<tr>
<td>Megalencephalic leukoencephalopathy with subcortical cysts 2A (MLC2A)</td>
<td>Remitting megalencephalic leukoencephalopathy with subcortical cysts 2A with or without intellectual disability</td>
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<tr>
<td>Megalencephalic leukoencephalopathy with subcortical cysts 2B (MLC2B)</td>
<td>Remitting megalencephalic leukoencephalopathy with subcortical cysts 2B with or without intellectual disability</td>
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<tr>
<td>Cystic leukoencephalopathy without megalencephaly</td>
<td>RNase T2-deficient leukoencephalopathy</td>
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<tr>
<td>Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)</td>
<td>Mitochondrial aspartyl-tRNA synthetase deficiency</td>
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*Continued*
### Metabolic and Heredodegenerative Disorders

#### Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)

- **Oxidative phosphorylation deficiency 12 (COXPD12)**
  - **#614924 Autosomal recessive EARS2 (16p12.2)**
  - Lesions in deep cerebral white matter, including thalami and hypothalami, as well as in brainstem and cerebellum, with sparing of the periventricular region, and thin posterior part of corpus callosum, lactate elevation in MR spectroscopy

#### Aicardi–Goutières syndrome

- **Leukodystrophy with calcification of the basal ganglia and lymphocytosis of CSF**
  - Prominent cerebral atrophy, calcifications in basal ganglia and cerebellar dentate nucleus, white matter lesions with temporal predominance, brainstem involvement possible

#### Cerebroretinal microangiopathy with calcifications and cysts (CRMCC)

- **Coats plus syndrome #612199 Autosomal recessive CTC1 (17p13)**
  - Intracranial calcifications and cysts involving deep grey nuclei, brainstem, cerebral and cerebellar white matter, and dentate nuclei

#### Sjögren-Larsson syndrome (SLS)

- **Fatty aldehyde dehydrogenase (FALDH) deficiency #270200 Autosomal recessive ALDH3A2 (17p11)**
  - Cerebral dysmyelination with periventricular predominance, brainstem involvement possible

#### Cerebrotendinous xanthomatosis (CTX)

- **Van Bogaert–Scherer–Epstein disease #213700 Autosomal recessive CYP27A1 (2q35)**
  - Dysmyelination with posterior predominance, cerebellum, brainstem and spinal involvement, brain and cerebellar atrophy, non-calcifying lesions in basal ganglia, calcifications possible

#### L-2-hydroxyglutaric aciduria

- **#236792 Autosomal recessive L2HGDH (14q21)**
  - Cerebral dysmyelination with subcortical predominance, cerebellar abnormalities in the dentate nucleus, cerebellar atrophy possible

### HYPOMYELINATING LEUKODYSTROPHIES

#### Pelizaeus–Merzbacher disease (PMD)

- **Hypomyelinating leukodystrophy-1 (HLD1) 312080 X-linked recessive PLP1 (Xq22)**
  - Diffuse and homogeneous hypomyelination, cerebellar and brainstem involvement, cerebellar atrophy possible

### Table 10.3 Classification of the demyelinating/dysmyelinating and hypomyelinating leukodystrophies according to genetic defects (continued)
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<td>Pelizaeus-Merzbacher-like disease type 1 (PMLD1)</td>
<td>Hypomyelinating leukodystrophy-2 (HLD2)</td>
<td>608804</td>
<td>Autosomal recessive</td>
<td>GJC2/GJA12 (1q41)</td>
<td>Similar to PML</td>
<td>Similar to PML with peripheral neuropathy and sporadic seizures</td>
</tr>
<tr>
<td>Hypomyelinating leukodystrophy-3 (HLD3)</td>
<td></td>
<td>260600</td>
<td>Autosomal recessive</td>
<td>AIMPI (4q24)</td>
<td>White matter involvement secondary to neuronal involvement</td>
<td>Prominent signs of grey matter involvement, such as early and severe brain atrophy with microcephaly, early onset epilepsy and severe intellectual disability</td>
</tr>
<tr>
<td>Hypomyelinating leukodystrophy 4 (HLD4; MIM #612233)</td>
<td>Mitochondrial HSP60 chaperonopathy, MitCHAP60 disease</td>
<td>#612233</td>
<td>Autosomal recessive</td>
<td>HSPD1 (2q33.1)</td>
<td>White matter involvement secondary to neuronal involvement</td>
<td>Signs of prominent grey matter involvement</td>
</tr>
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<td>Hypomyelination with atrophy of basal ganglia and cerebellum (HABC)</td>
<td>Hypomyelinating leukodystrophy-5 (HLD5)</td>
<td>#610532</td>
<td>Autosomal recessive</td>
<td>FAM126A (7p15.3)</td>
<td>Thin corpus callosum</td>
<td>Cataracts, PNS involvement possible</td>
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<tr>
<td>Hypomyelination with atrophy of basal ganglia and cerebellum (HABC)</td>
<td>Hypomyelinating leukodystrophy-6 (HLD6)</td>
<td>#612438</td>
<td>Mostly sporadic, due to de novo heterozygous mutations</td>
<td>TUBB4A (19p13)</td>
<td>Atrophy of the cerebellar vermis, small or absent putamen</td>
<td>Extrapyramidal signs such as rigidity, dystonia and choreoathetosis</td>
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<td>Hypomyelinating leukoencephalopathy with ataxia and delayed dentition</td>
<td>Ataxia, delayed dentition, and hypomyelination (ADDH) Hypomyelinating leukoencephalopathy with hypodontia and hypogonadotropic hypogonadism (4H syndrome) Hypomyelinating leukodystrophy 7 (HLD7)</td>
<td>#607694</td>
<td>Autosomal recessive</td>
<td>POLR3A (10q22.3)</td>
<td>Cerebellar atrophy, thin corpus callosum, (relative) T2 hypointensity of dentate nuclei, optic radiation, globus pallidus, anterolateral nuclei of thalami, and posterior limb of internal capsule</td>
<td>Dental abnormalities (possible), hypogonadotropic hypogonadism (possible), severe myopia (possible), PNS involvement (possible)</td>
</tr>
<tr>
<td>Hypomyelinating leukodystrophy-8 (HLD8)</td>
<td>Hypomyelinating leukodystrophy-8 with or without hypodontia and/or hypogonadotropic hypogonadism.</td>
<td>#614381</td>
<td>Autosomal recessive</td>
<td>POLR3B (12q23)</td>
<td>Cerebellar atrophy, thin corpus callosum, relative T2 hypointensity of dentate nuclei, optic radiation, globus pallidus, anterolateral nuclei of thalami, and posterior limb of internal capsule</td>
<td>Dental abnormalities possible, hypogonadotropic hypogonadism possible, severe myopia possible, PNS involvement possible</td>
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<td>Allan-Herndon-Dudley syndrome (AHDS)</td>
<td>Monocarboxylate transporter 8 deficiency, triiodothyronine (T3) resistance</td>
<td>#300523</td>
<td>X-linked recessive</td>
<td>SLC16A2 (Xq13)</td>
<td>Hypomyelination improving over time</td>
<td>X-linked severe intellectual disability with hypotonia</td>
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Table 10.3: Classification of the demyelinating/dysmyelinating and hypomyelinating leukodystrophies according to genetic defects (continued)
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<td>18q- syndrome</td>
<td>Chromosome 18q deletion syndrome</td>
<td>#601808</td>
<td>Autosomal dominant</td>
<td>MEBP (18q23)</td>
<td>MR imaging: hypointensity of globus pallidi, thin corpus callosum</td>
<td>Dental, hand and foot abnormalities, microcephaly, multiple malformations, short stature, endocrine abnormalities</td>
</tr>
<tr>
<td>#602100</td>
<td>Autosomal dominant</td>
<td></td>
<td></td>
<td></td>
<td>Surgically proved hydrocephalus, computed tomography (CT) scan of brain, plain radiographs of long bones, lateral X-rays of skull, and plain radiographs of short bones.</td>
<td></td>
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<tr>
<td>#257880</td>
<td>Autosomal recessive</td>
<td></td>
<td></td>
<td></td>
<td>MR imaging: hypointensity of globus pallidi, thin corpus callosum</td>
<td>Dental, hand and foot abnormalities, microcephaly, multiple malformations, short stature, endocrine abnormalities</td>
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<tr>
<td>#604569</td>
<td>Autosomal recessive</td>
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<td></td>
<td></td>
<td>MR imaging: hypointensity of globus pallidi, thin corpus callosum</td>
<td>Dental, hand and foot abnormalities, microcephaly, multiple malformations, short stature, endocrine abnormalities</td>
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<td>MR imaging: hypointensity of globus pallidi, thin corpus callosum</td>
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<td>Dental, hand and foot abnormalities, microcephaly, multiple malformations, short stature, endocrine abnormalities</td>
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<tr>
<td>Name</td>
<td>Alternative names</td>
<td>MIM no.</td>
<td>Mode of inheritance</td>
<td>Gene (chromosome)</td>
<td>Associated MRI features</td>
<td>Associated clinical features</td>
</tr>
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<td>-------------------------------------------------------</td>
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<td>Cockayne syndrome B (CSB)</td>
<td></td>
<td>#133540</td>
<td>Autosomal recessive</td>
<td><em>ERCC6</em> (10q11)</td>
<td>Similar to CSA</td>
<td>Similar to CSA</td>
</tr>
<tr>
<td>Xeroderma pigmentosum G/</td>
<td></td>
<td>#278780</td>
<td>Autosomal recessive</td>
<td><em>ERCC5</em> (13q33)</td>
<td>Similar to CS</td>
<td>Similar to CS with cutaneous features (photosensitive lesions)</td>
</tr>
<tr>
<td>Cockayne syndrome (XPG/CS)</td>
<td></td>
<td>#610651</td>
<td>Autosomal recessive</td>
<td><em>ERCC3</em> (2q21)</td>
<td>Similar to Cockayne syndrome</td>
<td>Similar to CS with cutaneous features (photosensitive lesions)</td>
</tr>
<tr>
<td>Xeroderma pigmentosum B/</td>
<td></td>
<td>#278760</td>
<td>Autosomal recessive</td>
<td><em>ERCC4</em> (16p13)</td>
<td>Similar to Cockayne syndrome</td>
<td>Similar to CS with cutaneous features (photosensitive lesions)</td>
</tr>
<tr>
<td>Cockayne syndrome (XPB/CS)</td>
<td></td>
<td>#601675</td>
<td>Autosomal recessive</td>
<td><em>ERCC2/XPD</em> (10q13)</td>
<td>Hypomyelination with periventricular predominance, homogeneous involvement of the corpus callosum, and sparing of U-fibres</td>
<td>Brittle and fragile hair, ichthyosis, nail abnormalities + clinical data</td>
</tr>
<tr>
<td>Trichothiodystrophy with photosensitivity (TTDP)</td>
<td></td>
<td></td>
<td></td>
<td><em>ERCC3/XPB</em> (2q14)</td>
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<td></td>
<td></td>
<td><em>GTF2H5</em> (6q25)</td>
<td></td>
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<tr>
<td>Hypomyelination with brainstem and spinal cord</td>
<td>DARS-related hypomyelination</td>
<td>#615281</td>
<td>Autosomal recessive</td>
<td><em>DARS</em> (2q21.3)</td>
<td>Hypomyelination involving the supratentorial white matter, brainstem, cerebellar peduncles, and dorsal columns and lateral corticospinal tracts of the spinal cord</td>
<td>Severe spasticity predominant in lower limbs, posterior column dysfunction</td>
</tr>
<tr>
<td>involvement and leg spasticity (HBSL)</td>
<td></td>
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<tr>
<td>RARS-related hypomyelination</td>
<td></td>
<td></td>
<td></td>
<td><em>RARS</em> (5q35)</td>
<td>Similar to HBLS, but without brainstem and spinal involvement</td>
<td>Similar to HBLS with severe spasticity predominant in lower limbs, but without brainstem and spinal signs</td>
</tr>
<tr>
<td>Global cerebral hypomyelination</td>
<td>Aspartate-glutamate carrier 1 (AGC1) deficiency</td>
<td>#612949</td>
<td>Autosomal recessive</td>
<td><em>SLC25A12</em> (2q31.1)</td>
<td>Cerebral hypomyelination and atrophy, no involvement of cerebellum or brainstem, decreased NAA in MR spectroscopy</td>
<td>Signs of prominent grey matter involvement</td>
</tr>
<tr>
<td>Deafness, dystonia, and cerebral hypomyelination</td>
<td></td>
<td>#300475</td>
<td>X-linked recessive</td>
<td><em>BCAP31</em> (Xq28)</td>
<td>Hypomyelination with variable cerebral or cerebellar atrophy</td>
<td>Dysmorphic facial features, severe psychomotor delay, sensorineural deafness, dystonia</td>
</tr>
<tr>
<td>(DDCH)</td>
<td></td>
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can be determined directly by DNA techniques. In addition, two non-allelic forms of MLD exist: MLD due to saposin B deficiency (MIM #249900) and multiple sulphatase deficiency or juvenile sulphatidosis (MIM #272200), a disorder that combines features of a mucopolysaccharidosis with those of metachromatic leukodystrophy (see Multiple Sulphatase Deficiency section).

Three clinical types of MLD can be distinguished according to age at onset: late infantile type (40%), juvenile type (40%) and adult type (20%). The late infantile form is the most homogeneous group, which presents between the ages of 6 months and 2 years. Children show delayed development or deterioration of walking, some being never able to walk alone. The gait is characterised by spasticity and ataxia. Ankle reflexes may be absent, contrasting with the presence of a bilateral Babinski sign. Later in the course of the illness, optic atrophy and more generalised spasticity dominate the clinical picture (MacFaul et al. 1982). The prognosis is poor, with death occurring before the age of 10 years.

The juvenile type varies in onset and may show symptoms as early as 4–6 years. Gait disorders combined with learning and behavioural problems can be observed. Motor signs include cerebellar and pyramidal dysfunction as well as signs of a peripheral neuropathy. Seizures and dementia are late manifestations. In adult cases, gait disorders, extrapyramidal symptoms and a psychiatric symptomatology dominate the clinical picture.

MLD should be suspected in all children with a progressive spastic–ataxic disorder and the paradoxical finding of a negative Achilles tendon reflex in the presence of exaggerated patellar tendon reflexes and Babinski sign. Fundi may show optic atrophy. The EEG is usually normal or may show some slow activity and epileptiform discharges late in the disease. The electroretinogram is preserved. Sensory and particularly motor nerve conduction velocities are decreased. In almost all cases there is an increased protein level in cerebrospinal fluid (CSF). In all three types, computed tomography (CT) and MRI show changes in the periventricular white matter with a frontal predominance (Fig. 10.1). U-fibres are spared, the corpus callosum is affected early during the disease, and pyramidal tracts may show signs of demyelination in juvenile and adult cases. The diagnosis is confirmed by measurement of ARSA and the demonstration of metachromatic material in urine.

No effective treatment is yet available. Bone marrow or haematopoietic stem cell transplantation has been tried with conflicting results. The supplementation of aryl-sulphatase A has been discussed (Matzner and Gieselmann 2005). Most recently cord blood transplant (Pierson et al. 2008) and lentiviral haematopoietic stem cell (HSC) gene therapy (Biffi et al. 2013) have been reported to stop disease progression in presymptomatic MLD cases.

**METACHROMATIC LEUKODYSTROPHY DUE TO SAPOSIN B DEFICIENCY**

Rare cases of MLD (MIM #249900) are caused by a mutation involving an activator protein (saposin B) that is encoded by the gene PSAP on chromosome 10q22.1 (Henseler et al. 1996; Wiobe et al. 2000; Kuchar et al. 2009). The activator protein activates not only the hydrolysis of sulphatides by ARSA but also the hydrolysis of GM1-gangliosides. Deficiency of saposin B may result in a juvenile or rarely a late infantile phenotype of MLD but which histologically also showing storage of gangliosides. The diagnosis can be confirmed in fibroblast cultures: pathological sulphatide metabolism can be corrected by the activator protein (Inui et al. 1983).

**MULTIPLE SULPHATASE DEFICIENCY**

**Mucosulfatidosis; Juvenile Sulfatidosis of Austin type**

Multiple sulphatase deficiency (MSD; MIM #272200) is a rare autosomal recessive disorder, combining features of both MLD and mucopolysaccharidosis, caused by the absence of arylsulphatase A, B and C and mucopolysaccharide sulphatidase activity. It is caused by homozygous or compound heterozygous mutations in the sulphatase-modifying factor-1 gene (SUMF1) on chromosome 3p26 (Cosma et al. 2003; Dierks et al. 2003). As a result of the deficit, patients accumulate sulphatides and mucopolysaccharides in viscera and brain and there is an increased excretion of heparan sulphate in urine. Clinical manifestations include coarse features, short stature, hepatosplenomegaly combined with skeletal changes, progressive neurodevelopmental deterioration and peripheral neuropathy. There is no corneal clouding. Three subtypes (neonatal, early childhood and juvenile) can be distinguished. Children with the most frequently occurring early childhood form learn to walk but develop a progressive encephalopathy combined with a peripheral neuropathy and the described somatic features around the age of 2 years. Progressive deterioration leads to early death. The diagnosis can be suspected in patients with neurological symptoms combined with skeletal
dysplasia on X-ray and finally confirmed by the demonstration of arylsulphatase A, B and C deficiency. X-rays of the lumbar spine may show anterior beaking or ovoid vertebrae as in classic MPS disorders. Cranial MRI showing white matter changes similar to those in MLD.

**GLOBOID CELL LEUKODYSTROPHY**

**Krabbe Disease**

Globoid cell leukodystrophy (GLD; MIM #245200) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme galactocerebrosidase-beta-galactosidase (galactocerebrosidase) (Suzuki et al. 1971). It is due to homozygous or compound heterozygous mutations in the galactosylceramidase (GALC) gene on chromosome 14q31.3 (Sakai et al. 1994). Galactocerebrosides are the most specific myelin lipids in the brain; their concentration reflects maturation. Three subtypes of GLD have been delineated: the most common infantile form, and rare juvenile and adult subtypes. The neuropathology of Krabbe disease is characterised by a paucity of oligodendrocytes, lack of myelin and proliferation of glial cells in affected areas with mononuclear epithelioid cells and clusters of large multinucleated globoid cells. Involvement of the peripheral nervous system is common but may be less pronounced than in MLD. The deficiency of galactocerebrosidase-beta-galactosidase results in accumulation of cerebrosides and psychosine (galactosyl sphingosine). Many symptoms observed in GLD are related to the increase of psychosine, which acts as a toxic substance (Suzuki 2003).

The most common infantile form presents initially with hypotonia before 6 months of age. In addition, extreme irritability, especially marked sound-induced startle and progressive stiffness, are characteristic early symptoms. Increased muscle tone and pyramidal tract signs are found on examination, and opisthotonic spasms with head retraction are often precipitated by external stimuli. Convulsions are frequent and may present as infantile spasms with atypical hypersarrhythmic EEG patterns. Absence of deep tendon reflexes frequently contrasts with the spasticity. Optic atrophy and blindness develop. The disease is rapidly progressive and death usually occurs before the age of 2 years. The clinical stages of Krabbe disease have been delineated by Hagberg et al. (1969).

In all infantile cases, high CSF protein (above 70mg/dL) is found and nerve conduction velocities are decreased. In late-onset forms of GLD, CSF protein may be normal. Hyperintensities in brainstem, cerebellum, internal capsule, thalamus and basal ganglia have been found on CT. MRI detects T1 hypointensity and T2 hyperintensity in cerebral and cerebellar white matter with periventricular and parieto-occipital predominance (Fig. 10.2). Magnetic resonance spectroscopy reveals pronounced elevation of myo-inositol and choline-containing compounds in affected white matter, reflecting demyelination and glial proliferation, accompanied by a decrease of N-aspartyl acetate as a sign of neuro-axonal loss (Brockmann et al. 2003a).

The diagnosis of GLD is based on the characteristic clinical symptoms, raised CSF protein and MRI findings. In late-onset cases, symptoms are less characteristic and include walking difficulties, fading vision, and learning problems. In any leukodystrophy combined with a mild peripheral neuropathy, GLD must be suspected. Treatment is symptomatic. High doses of benzodiazepines may be useful in relieving the extreme irritability and opisthotonus. Haematopoietic stem cell transplantation has been tried with doubtful results (Krivit et al. 1998). Transplantation of umbilical cord blood from unrelated donors has been found to restore normal blood levels of galacto-cerebrosidase and to stop the progression of the disease in presymptomatic patients (Escolar et al. 2005; Prasad et al. 2008).

**X-LINKED ADRENOLEUKODYSTROPHY**

Addison Disease and Cerebral Sclerosis; Melanodermic Leukodystrophy; Siemerling-Creutzfeldt Disease; Bronzed Schilder Disease

X-linked adrenoleukodystrophy (X-ALD; MIM #300100) is the most frequently occurring leukodystrophy in males,
with an estimated incidence of 1: 20,000. The disorder was initially described as ‘encephalitis periaxialis diffusa’ by Schilder in 1913 and in a case report of ‘diffuse sclerosis’ combined with adrenal atrophy by Siemerling and Creutzfeldt in 1923. More than half a century later, the defect in peroxisomal beta-oxidation leading to characteristic excess of very long chain fatty acids in plasma, blood cells and altered fibroblasts was discovered (Igarashi et al. 1976; Moser et al. 1980). The gene for X-ALD, ABCD1 gene, has been mapped to Xq28 and found to encode a peroxisomal membrane protein of the ATP-binding cassette (ABC) transporter family (Moser et al. 1993). More than 200 mutations have been identified.

The transporter is necessary for transferring very long chain fatty acids (VLCFAs) or VLCFA-CoA into the peroxisomes, where they are metabolised. This process depends on a number of peroxisome biogenesis genes or peroxines (PEX). No correlation has been found between the nature of a mutation and the clinical phenotype (Powers and Moser 1998; Dubois-Dalcq et al. 1999).

A selective susceptibility of adrenal glands and neuronal tissue, with lesions especially involving the spinal cord and brain, is the morphological hallmark of X-ALD. In contrast to the adult adrenomyeloneuropathy (AMN), the childhood form of X-ALD is associated with an inflammatory reaction in the cerebral white matter. There is a confluent loss of myelin, usually symmetrical and most prominent in the parieto-occipital regions. U-fibres are relatively spared, but corpus callosum, the posterior part of the internal capsule, the corticospinal tract, the pons and the medulla are also involved.

Histological study reveals a loss of myelinated axons and oligodendrocytes, reactive astrocytosis and later cavitations and astrogliosis. The active edge of demyelination showing intensive perivascular inflammation and accumulation of lipophages. Perivascular cell collections contain macrophages and particularly lymphocytes. Hypertrophic GFAP-positive astrocytes and macrophages express cytokines like tumour necrosis factor alpha (TNF-alpha) and interleukin 1 (IL-1).

Three main phenotypes of X-ALD occur in males and three further subtypes are known (van Geel et al. 1994; Bezman and Moser 1998; Kirk et al. 1998; Ruiz et al. 1998; Bezman et al. 2001). Heterozygous female carriers of the mutated gene may be symptomatic, mainly in the following forms of AMN:

1. The cerebral childhood form (frequency 30–40%): onset by 3–10 years of age, rapidly progressive.
2. Adolescent ALD (4–7%): onset by age 11–21 years, slower progression.
3. Adult AMN (25–40%): onset by mean age 28 years (SD 9 years), spinal cord involvement.
4. Adult ALD (2–5%): marked by psychiatric symptoms and dementia.
5. Addison disease only (10–15%): onset before 7–8 years; most patients eventually develop AMN, the frequency of which varies with age.
6. Asymptomatic cases (5–15%): biochemical and genetic defect only.

The cerebral childhood form of ALD has an initial slowly progressing phase followed by rapid deterioration. Initial symptoms are difficulties at school, combined with behavioural disturbances. Impaired hearing or hearing loss may be an early symptom. Impaired vision, dementia, seizures, and difficulties in walking, speech and handwriting develop fast following the onset of first neurological symptoms. Once neurological symptoms become manifest, progression is rapid and an apparent vegetative state develops in a few years. Mean age at death was 9.4 years (SD 2.7 years, range 5.1–19 years) in a series of patients reported from the Kennedy Krieger Institute in the USA (Powers and Moser 1998).

Hyperpigmentation typical for Addison disease may be present before neuropsychological disturbances occur.

X-linked ALD must be excluded in every boy with adrenal insufficiency. The diagnosis is based on the demonstration of increased concentrations of VLCFA (c22:0, c24:0, c26:0) in plasma. Prenatal diagnosis is possible by measurements of VLCFA in cultured amniocytes and mutation analysis. The demonstration of cerebral demyelination by MRI is of great value and in many cases almost diagnostic. Cerebral demyelinating lesions usually start in the splenium of the corpus callosum and slowly progress symmetrically into the parieto-occipital white matter. Arcuate fibres are spared (Fig. 10.3). Using contrast agents the most severely affected area of the brain showing a rim of enhancement. The posterior limb of the internal capsule, pyramidal tract, pons and brainstem may also be involved. In about 10% of cases, demyelination may also start frontally with involvement of the anterior limb of the internal capsule. Symmetrical involvement of the cerebellar white matter is also possible. The differential diagnosis of X-ALD includes among others: brain tumour, other leukodystrophies, encephalitis, subacute sclerosing panencephalitis, multiple sclerosis and acute demyelinating encephalitis.

Adrenal insufficiency can be effectively corrected by hormone replacement, but substitution does not prevent or alter the neurological manifestations. A diet with unsaturated fatty
acids (Lorenzo’s oil) lowers the plasma levels of VLCFA in patients with X-ALD (Kolodny 1987). However, the clinical results are disappointing when given to symptomatic patients (Aubourg et al. 1993). A follow-up study of 49 asymptomatic patients with ALD treated with Lorenzo’s oil was able to show a reduced risk of developing MRI abnormalities (Moser et al. 2005). The most effective treatment so far has been the haematopoietic stem cell transplantation in the early stage of the disease (Shapiro et al. 2000; Peters et al. 2004). More recently, possible clinical benefits of lentiviral-mediated gene therapy of haematopoietic stem cells have been reported (Cartier et al. 2009).

**OTHER PEROXISOMAL DISORDERS**

Peroxisomal disorders can be classified into two main groups: (1) disorders of peroxisome biogenesis and (2) single peroxisomal enzyme deficiencies (see Chapter 9). A peroxi-

somal disorders classification according to genetic defects is shown in Table 10.4.

The peroxisome biogenesis disorders (PBDs) are a group of autosomal recessive disorders affecting the formation of functional peroxisomes. They can be caused by mutations in any of several genes, known as pexins (PEX), involved in peroxisome biogenesis (Eggerink et al. 2011). PBDs can be classified into four phenotypes. Three of them, Zellweger syndrome, neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD), constitute a spectrum of overlapping features (Zellweger syndrome spectrum [ZSS]), with the most severe being the Zellweger syndrome and the least severe infantile Refsum disease. The fourth, rhizomelic chondrodysplasia punctata (RCDP1), constitutes a distinct PBD phenotype.

ZSS is characterised by multiple organ dysfunction, sensoryneural hearing loss, pigmentary retinal degeneration, and psychomotor impairment. Zellweger syndrome, the most severe form, is characterised by neonatal onset with neuronal migration defects, dysmorphic craniofacial features, large fontanelle, severe hypertonia, neonatal seizures, skeletal abnormalities (patellar calcifications) and liver dysfunction, and is fatal in early life. NALD and IRF constitute milder forms resulting in a more varied initial presentation and natural history. Progressive sensoryneural hearing loss, retinal dystrophy and developmental delay are seen in older children. MRI findings in ZSS include, in addition to dysmyelination, brain atrophy and neuronal migration defects resulting in polymicrogyria, pachygyria and heterotopias. Concerning diagnosis, measurement of plasma VLCFA levels is the most commonly used and most informative initial screen. Biochemical abnormalities should be confirmed in cultured fibroblasts or by mutation analysis.

RCDP1 is characterised by skeletal abnormalities with severe shortening of the proximal parts of the extremities, microcephaly, characteristic facial features, cataracts, severe intellectual disability and spasticity, most patients dying in the first decade of life. MRI findings may include supratentorial white matter abnormalities with parieto-occipital predominance. Biochemically, plasmalogen synthesis and phytanic acid alpha-oxidation are defective, while plasma VLCFA are normal.

The second group includes disorders in which the defect involves a single peroxisomal protein but the structure of the peroxisome is intact. Most of them are due to single defects in proteins involved in peroxisome fatty acid beta-oxidation. The paradigm of these disorders is X-ALD (MIM #300100; see X-linked Adrenoleukodystrophy section). Peroxisomal acyl-CoA oxidase deficiency, also called pseudoneonatal adrenoleukodystrophy (pseudo-NALD; MIM #264470), is a rare autosomal recessive neurodegenerative disorder caused by mutations in the ACOX1 gene (17q25.1) encoding peroxisomal straight-chain acyl-CoA oxidase (Ferdinandusse et al. 2007). To date, only 30–40 cases have been described. Clinical onset occurs in the neonatal period with characteristic facial features, hypotonia and seizures as dominant features. In the course of the disease, developmental delay, hypertonia with hyper-reflexia, neurosensorial hearing loss and retinal dystrophy may occur. MRI showing atrophy and white matter abnormalities in the ponto-medullary cortico-spinal tracts and in the cerebellar and cerebral white matter. Diagnosis is based on the demonstration of increased serum VLCFA and markedly reduced acyl-CoA oxidase activity in fibroblasts, and can be confirmed by mutation analysis. Similar manifestations have been described in D-bifunctional protein deficiency (MIM #261515) caused by mutations in the HSD17B4 gene on chromosome 5q23.1 (van Grunsven et al. 1998). Alpha-methylacyl-CoA racemase (AMACR) deficiency (MIM #614307) is caused by homoyzogous mutations in the AMACR gene on chromosome 5p13.2 (Ferdinandusse et al. 2000). It is clinically characterised by learning disability and seizures that may be present since childhood, and later on visual impairment, sensorimotor neuropathy, spasticity and migraine. Brain MRI showing white matter involvement. Serum pristanic acid and C27 bile acid intermediates are increased. Sterol carrier protein 2 (SCP2) deficiency, also known as leukoencephalopathy with dystonia and motor neuropathy (MIM #613724), caused by homozygous mutation in the SCP2 gene on chromosome 1p32.3, has been described in one patient with juvenile clinical onset with torticollis and dystonic head tremor as well as slight cerebellar signs with intention tremor, nystagmus, hypomia, and azospermia, accumulation of branched-chain pristanic acid in plasma and abnormal bile alcohol glucuronides excreted in urine, and leukencephalopathy and involvement of the thalamus and pons on MRI (Ferdinandusse et al. 2006).

Some disorders are due to single defects in proteins involved in ether-phospholipid biosynthesis. Rhizomelic chondrodysplasia punctata type 2 (RCDP2; MIM #222765), caused by homozygous or compound heterozygous mutations in the DHAIP1 gene encoding the enzyme dihydroxyacetone-phosphate acyltransferase on chromosome 1q42.2 (Ofman et al. 1998), and rhizomelic chondrodysplasia punctata type 3
Part IV  Metabolic and Heredodegenerative Disorders

(RCDP3; MIM #600121), caused by homozygous or compound heterozygous mutations in the gene AGPS encoding the enzyme alkyldihydroxyacetonephosphate (alkyl-DHAP) synthase on chromosome 2q31.2 (Wanders et al. 1994), are part of this group. RCDP2 and RCDP3 are clinically similar to RCDP1. However, plasmalogen levels are reduced but phytanic acid levels and the processing of 3-ketothiolase are normal.

<table>
<thead>
<tr>
<th>Name</th>
<th>Phenotypes</th>
<th>MIM no.</th>
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<th>Gene (chromosome)</th>
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</table>

PBD, peroxisomal biogenesis disorder; ZS, Zellweger syndrome; AR, autosomal recessive; NALD/IRD, neonatal adrenoleukodystrophy/infantile Refsum disease; X-ALD, X-linked adrenoleukodystrophy; CCALD, cerebral childhood form of X-linked adrenoleukodystrophy; AdoALD, adolescent adrenoleukodystrophy; AAMN, adult adrenomyeloneuropathy; AALD, adult adrenoleukodystrophy; X-R, X-linked recessive; ACOX Def, peroxisomal acyl-CoA oxidase deficiency; PNALD, pseudoneonatal adrenoleukodystrophy; DBP Def, D-bifunctional protein deficiency; SCPx, sterol carrier protein 2 (SCPx) deficiency; AMACR Def, alpha-methylacyl-CoA racemase deficiency; RCDP, rhizomelic chondrodysplasia punctata; RD, classic/adult Refsum disease.
Lastly, there are single defects in proteins involved in fatty acid alpha-oxidation. Classic Refsum disease, also known as adult Refsum disease type 1 (MIM #266500) is the only known type in this group. It is caused by mutation in the gene \textit{PHYH/PAXH} encoding phytanoyl-CoA hydroxylase on chromosome 10p13 (Mihalik et al. 1997). Accumulation of phytanic acid leads to lesions essentially in retina, brain and peripheral nervous system. Clinical onset occurs usually in young adults, but its first signs may also appear during childhood, in the form of retinitis pigmentosa, and later on peripheral sensory–motor polyneuropathy, cerebellar ataxia and elevated protein levels in the CSF without an increase in the number of cells. Other features such as sensorineural hearing loss, anosmia, ichthyosis, skeletal abnormalities and cardiomyopathy may occur. Phytanic acid is increased in plasma and urines. As phytanic acid comes exclusively from food, a strict diet may reduce symptoms.

A phenotype clinically indistinguishable from that of classic Refsum disease, but with a different biochemical profile, is found in Refsum disease type 2 (MIM #614879), caused by mutations in the gene \textit{PEX7} on chromosome 6q23.

ALEXANDER DISEASE

Alexander disease (MIM #203450) is the first described disorder caused primarily by a dysfunction of astrocytes (Hanefeld 2004; Mignot et al. 2004). It was first described by Alexander in 1949 in an 18-month-old boy with macrocephaly. The neuropathological hallmark on examination was the presence of ‘rod-shaped fuscophil fibres’ in the white matter of his brain, which were later identified as Rosenthal fibres. Glial fibrillary acidic protein (GFAP) is present in high concentration in Rosenthal fibres and is therefore used as a histological marker. Heterozygous mutations, de novo in 95% of cases, of the gene \textit{GFAP} encoding glial fibrillary acidic protein, one of the major intermediate filament proteins of mature astrocytes, on chromosome 17q21 in patients with Alexander disease have subsequently been discovered to be the cause of this autosomal recessive disease (Brenner et al. 2001).

According to the clinical presentation three different types of Alexander disease can be distinguished: infantile, juvenile and adult cases. The most common infantile type belongs to the group of macrocephalic white matter diseases. Affected children are norencephalic at birth and develop a slowly progressive megalencephaly combined with symptoms of spasticity, irritability and epileptic seizures (Pridmore et al. 1993). Acute episodes of intracranial hypertension may be observed following mild head trauma. Death may occur before the age of 10 years. Apart from this infantile progressive type, Alexander disease has also been diagnosed in juvenile and adult patients. One peculiarity in the cases of older patients is the increasing involvement of brainstem and bulbar structures. Older patients are usually normocephalic. The disease has been reviewed by Mignot et al. (2004).

A more recent classification distinguishes Alexander disease type I, with onset in infancy with encephalopathy, epilepsy and failure to thrive and shorter survival (median 14 years), and Alexander disease type II, with onset throughout the lifespan (mean 21.64 years) with bulbar autonomic and motor signs and longer survival (median 25 years).

The diagnosis in classic cases of Alexander disease is based on the clinical presentation with macrocephaly, regression, seizures and the presence of bulbar symptoms in older patients. The EEG may show generalised slow activity and some focal discharges. The most important information is provided by cranial CT and MRI. Van der Knaap et al. (2001) described neuroradiological characteristics that are almost diagnostic for Alexander disease. These include extensive signal enhancement of cerebral white matter with frontal predominance, a periventricular rim with high signal on T1-weighted and a low signal on T2-weighted images, abnormalities in basal ganglia, thalamus and brainstem, and contrast enhancement of particular grey and white matter structures. Atypical MRI features have also been described (van der Knaap et al. 2005; van der Knaap et al. 2006a). MRS reveals a strong elevation of myo-inositol and a decline of N-acetylaspartic acid (NAA) (unlike in Canavan disease), accompanied by accumulation of lactate in affected cerebral and cerebellar white matter. Myo-inositol was elevated in white matter as well as in grey matter and in basal ganglia (Fig. 10.4). The pattern reflects glial (astrocytic)
proliferation as well as active demyelination and neuro-axonal degeneration. Increased levels of GFAP in CSF in all three subtypes of Alexander disease were described by Kyllerman et al. (2005). The diagnosis is confirmed by molecular genetic analysis of the \textit{GFAP} gene. Only symptomatic treatment is available for Alexander disease.

GIANT AXONAL NEUROPATHY 1

Autosomal recessive giant axonal neuropathy or giant axonal neuropathy 1 (GAN1; MIM #256850) is a severe neurodegenerative disorder of childhood with polyneuropathy that affects both the peripheral and central nervous systems and is accompanied by characteristically kinky hair. Axonal loss and the presence of giant axonal swellings filled with neurofilaments on nerve biopsy are pathological hallmarks. Disorganisation of other members of the intermediate filament family of proteins is seen in other tissues such as keratine, which explains the characteristic kinky feature of hair. GAN1 is caused by homozygous or compound heterozygous mutations in the gene \textit{GAN} encoding gigaxonin, a protein involved in neurofilament architecture, on chromosome 16q23 (Bomont et al. 2000). Patients usually present with loss of intellectual capacity, epilepsy and cerebellar and pyramidal tract signs during early childhood. The disease progresses rapidly and children soon become bedridden and death occurs usually by late adolescence. However, phenotypic variability, even among patients with the same mutation, has been reported (Tazir et al. 2009), with age at onset ranging from birth to 7 years and variable presence of intellectual disability, spasticity and hair abnormalities. Brain MRI showing abnormalities of the cerebellum and brain white matter. Diagnosis can be made by mutational analysis. Genetic counselling is advised for parents of an affected child. Prenatal diagnosis can be proposed. There is no specific treatment.

CANAVAN DISEASE

Canavan-Van Bogaert-Bertrand Disease; Spongy Degeneration of CNS; Aspartoacylase Deficiency

Canavan disease (MIM #271900) was first described in 1931 under the designation \textit{Schilders Encephalitis periaxialis diffusa} and in 1949 was recognised by van Bogaert and Bertrand as a rare autosomal recessive disease entity including leukoencephalopathy and macrocephaly. In 1988 a deficiency of aspartoacylase (Matalon et al. 1989) leading to an increased concentration of NAA in urine and plasma was correlated with Canavan disease. The genetic defect is caused by mutations in the gene for aspartoacylase (\textit{ASPA}) located on chromosome 17p13.2 (Kaul et al. 1993). Canavan disease is also characterised by macrocephaly combined with hypotonia, irritability and feeding difficulties. Patients suffering from the most frequent infantile type develop spasticity and blindness, and death occurs before 3 years of age. A severe congenital form resembles a metabolic encephalopathy, while the very rare juvenile form has a normal head circumference and showing a more protracted course. Neuropathology is characterised by degeneration and rarefaction of neural tissue (status spongiosus).

The cranial CT showing diffuse symmetrical hypodensity of white matter; MRI reveals a centripetal pattern of demyelination starting in the U-fibres and progressing to the periventricular regions (Fig. 10.5). As one of the major metabolites detected by MRS, NAA showing an increased signal in the brain of patients with Canavan disease (Grod et al. 1990). The increased concentration of NAA in proton magnetic resonance spectra of the brain is almost diagnostic for the disease. The diagnosis is confirmed by the demonstration of increased concentrations of NAA in plasma and urine and a mutation in the gene of aspartoacylase.
Prenatal diagnosis is possible in cultured amniocytes. The course is progressive, although the rate of progression may be variable (Traeger and Rapin 1998). There is no known treatment.

**LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER**

**Vanishing White Matter Disease; Vanishing White Matter Leukodystrophy; Childhood Ataxia with CNS Hypomyelinisation; Myelinopathia Centralis Diffusa**

This disorder, now called vanishing white matter disease or leukencephalopathy with vanishing white matter (VWM; MIM #603896), represents one of the most prevalent inherited childhood white matter disorders (van der Knaap et al. 2006b). Following the description in earlier case reports, the disease was described in 1993 by Hanefeld et al. as diffuse white matter disease with unique features on MRI and proton MRS. These authors described three children, including male and female siblings, who developed ataxia following a mild head trauma and a nonspecific infection respectively. The third patient, a boy, became ataxic following mild head trauma. Ataxia persisted over three days. A CT taken at the time showed diffuse white matter changes. The boy made an initial recovery but became ataxic again following mild head traumas or nonspecific febrile illness. At the age of 4 years, he was referred with a spastic–ataxic gait, brisk reflexes, clonus and bilateral Babinski signs. During the following months and years he developed optic atrophy, swallowing difficulties and major seizures. He later died from bronchopneumonia. His sister followed almost the same clinical course. MRI in both siblings showed almost identical diffuse white matter abnormalities. The MRS done at the same time revealed a complete loss of all metabolites in affected white matter, while brain spectra of grey matter revealed only mild but definite decrease of NAA. The MRS appearance of white matter resembled CSF with a marked elevation of lactate (Fig. 10.6). Similar cases were described in large numbers during the following years (Schiffmann et al. 1994; van der Knaap et al. 1997). Leegwater et al. (2001a) and van der Knaap et al. (2002a) were able to demonstrate mutations in all five subunits of the eukaryotic translation initiation factor, eIF2B. Thus, VWM can be caused by homozygous or compound heterozygous mutations of EIF2B1 on chromosome 12q24, EIF2B2 on chromosome 14q24, EIF2B3 on chromosome 1p34, EIF2B4 on chromosome 2p23 or EIF2B5 on chromosome 3q27.

Further studies showed that early-onset variants including the Cree-leukoencephalopathy (Black et al. 1988) are caused by a mutation in EIF2B5 (Fogli et al. 2002a, b). This mutation has also been described in other cases with a severe, lethal ante- and perinatal onset of the leukencephalopathy. In addition other abnormalities are often present such as oligohydramnios, intrauterine growth retardation, cataract, pancreatitis, hepatosplenomegaly, hypoplasia of kidneys and ovarian dysgenesis (van der Knaap et al. 2003a). The combination of white matter disease with ovarian dysgenesis had already been described by Schiffmann et al. (1997). It has now become obvious that eIF2B disorders, as they are now called, show a wide spectrum of clinical manifestations, from the rare acute early-onset types, the classic VWM syndrome, to milder late-onset and adult cases (Fogli and Boespflug-Tanguy 2006; van der Knaap et al. 2006b).

Neuropathological investigations have demonstrated age-dependent abnormalities. Cystic cavitations are described in advanced cases. Microscopically there is a loss of myelin but no inflammatory reaction. Grey matter is generally spared but axonal loss in areas of cavitation is complete. Oligodendrocytes are severely affected, showing apoptosis in early-onset cases (Brück et al. 2001) and increased density of oligodendrocytes in long-standing cases (Rodriguez et al. 1999; Van Haren et al. 2004). A study of cell cultures from the brain of a boy who died at the age of 12 years showed in vitro a rapid generation of oligodendrocytes but a severely compromising reduction of GFAP-positive astrocytes. A deficiency of normal astrocyte
function may, therefore, be involved in the pathogenesis of VWM.

The diagnosis in the classic type of VWM is based on the clinical presentation and course: normal early development during the first 2–3 years, followed by ataxia and spasticity, usually in the context of mild trauma or nonspecific febrile illness, rapid progression with loss of motor function, seizures and late cognitive deterioration. There are no signs of peripheral neuropathy. Alternatively, recovery, often only partial, may occur with later recurrences leading to progressive decline.

MRI showing diffuse white matter disease with a characteristic early involvement of the central segmental tract. MRS confirms a loss of myelin, revealing a metabolic pattern, different from CSF only by the presence of lactate. The disease progresses to severe disability and most children with the classic phenotype die before the age of 20 years.

An elevation of glycine and a decreased concentration of asialotransferrin have been described as a possible marker of the disease (van der Knaap et al. 1999). However, MRI criteria, as formulated by van der Knaap, are primarily used for diagnosis (van der Knaap et al. 1998). In view of the wide phenotypic variability in eIF2B disorders the diagnosis has to be confirmed by genetic analysis. Prenatal diagnosis of eIF2B disorders is available. No treatment is known.

MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 1

Vacuolating Megalencephalic Leukoencephalopathy with Subcortical Cysts; Leukoencephalopathy with Swelling and Cysts; Van Der Knaap Disease

Megalencephalic leukoencephalopathy with subcortical cysts 1 (MLC1; MIM #604004) was first described in 1995 by van der Knaap et al. as a ‘leukoencephalopathy with swelling and a discrepantly mild clinical course’ in eight children. Family studies suggested an autosomal recessive mode of inheritance; the MLC1 gene, coding for a transmembrane protein associated with Na,K-ATPase complex, was mapped to chromosome 22qter by Topçu et al. (2000) and identified by Leegwater et al. (2001b). The disease was characterised by megalencephaly and leukoencephalopathy, with onset during the first year of life and a slowly progressive neurological deterioration. Brain biopsy in one of the patients revealed a spongiform leukoencephalopathy with vacuolisation and splitting of the outer lamellae of the myelin sheaths (van der Knaap et al. 1995). Further cases with similar clinical presentation have been reported (Goutières et al. 1996; Singhal et al. 1996; Mejaski-Bosnjak et al. 1997; Topçu et al. 1998).

The clinical symptomatology consists of macrocephaly, ataxia, spasticity, seizures and mild intellectual deterioration.

Remarkably, cognitive functions are well preserved in many patients up to adolescence. The EEG may show epileptiform activity, a photoconvulsive response and generalised slowing (Topçu et al. 1998). The MRI reveals extensive signal changes of hemispherical white matter early in the disease and the development of subcortical cysts predominantly in the temporal and parietal regions.

Mejaski-Bosnjak et al. (1997) reported the MRS features of an 8-year-old girl with a severe clinical course of MLC that had led to wheelchair dependency at age 5 years. Localised MRS of the affected white matter showed a loss of all metabolites, pointing to a complete disintegration of neuro-axonal and glial tissue (Fig. 10.7). Brockmann et al. (2003b) reported a 37-year-old woman cognitively normal with increasing gait disturbance caused by spasticity and ataxia. MRI showed enlargement of ventricles and subarachnoid spaces. Cerebral white matter was characterised by diffuse T2-hyperintensity with numerous subcortical cysts present.

Diagnosis is based on clinical findings, in particular megalencephaly, well-preserved cognitive function and characteristic MRI images. No treatment for the disease is available.

MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 2

Megalencephalic leukoencephalopathy with subcortical cysts can also be caused by mutations in the HEPACAM gene, coding for a glial cell adhesion molecule, on chromosome 11q24.2 (Lopez-Hernandez et al. 2011). Two forms are known: megalencephalic leukoencephalopathy with subcortical cysts 2A (MLC2A, or remitting megalencephalic leukoencephalopathy with or without intellectual disability; MIM #613925), caused by homozygous or compound heterozygous mutations in the HEPACAM gene, and megalencephalic leukoencephalopathy with subcortical cysts 2B (MLC2B; MIM #613926), a similar, but less severe
disorder that showing improvement of MRI changes with age, caused by heterozygous mutations in the \textit{HEPACAM} gene.

MLC2A is an autosomal recessive disorder characterised by infantile-onset macrocephaly and later onset of motor deterioration, with ataxia and spasticity, seizures, and cognitive decline of variable severity. Brain MRI showing typical white matter abnormalities, including swelling of the cerebral white matter and subcortical cysts, in all stages of the disease.

MLC2B is an autosomal dominant disorder characterised by infantile onset of macrocephaly and mildly delayed motor development associated with white matter abnormalities on brain MRI that improve with age. About 40% of patients have intellectual disability.

**CYSTIC LEUKOENCEPHALOPATHY WITHOUT MEGALENCEPHALY**

\textbf{RNase T2-Deficient Leukoencephalopathy}

Cystic leukoencephalopathy without megalencephaly (MIM \#612951) is caused by a homozygous or compound heterozygous mutation in the ribonuclease T2 \textit{RNASET2} gene on chromosome 6q27 (Henneke et al. 2009). About 30 cases have been reported to date. It is a non-progressive infantile-onset encephalopathy with normo- or micro-cephaly and severe psychomotor impairment, accompanied by seizures and sensorineural hearing impairment. Brain MRI showing bilateral anterior temporal lobe cystic lesions and enlarged inferior horns combined with multifocal brain white matter alterations. CT has shown intracranial calcifications in some children. The main differential diagnosis is congenital cytomegalovirus infection (Olivier et al. 1998; Gomes et al. 2001; Henneke et al. 2005; Henneke et al. 2009).

**LEUKOENCEPHALOPATHY WITH BRAINSTEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION**

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL; MIM \#614924), also known as combined oxidative phosphorylation deficiency 12 (COXPD12), is caused by homozygous or compound heterozygous mutations in the \textit{EARS2} gene, coding for the mitochondrial glutamyl-tRNA synthetase 2, on chromosome 16p12.2 (Steenweg et al. 2012). Only few cases have been reported to date. Clinically there are two main phenotypes: the more severe phenotype is characterised by early onset after birth with hypotonia and lack of psychomotor development followed by a severe disease course with spastic tetraparesis, dystonia, visual impairment and seizures, resulting in marked disability; the milder phenotype is characterised by normal or mildly delayed early development with onset of regression later in the first year of life with spasticity, loss of milestones, and sometimes seizures and irritability, followed after age 2 years by clinical, biochemical and imaging improvement. Laboratory studies show intermittent increases of serum transaminases, increased alpha-fetoprotein, increased serum lactate, and muscle biopsy demonstrates cytochrome C oxidase (COX) deficiency. MRI showing T2-weighted hyperintensities of the deep cerebral white matter, including the thalami and hypothalami, as well as in the brainstem and cerebellum, with sparing of the periventricular region, and thin posterior part of the corpus callosum. MRS showing increased lactate in the cerebral white matter.

**LEUKODYSTROPHY WITH CALCIFICATION OF THE BASAL GANGLIA AND LYMPHOCYTOSIS OF CSF**

\textbf{Aicardi–Goutières Syndrome}

Aicardi–Goutières syndrome (AGS) is a genetically heterogeneous encephalopathy characterised in its most severe form by cerebral atrophy, leukodystrophy, intracranial calcifications, chronic CSF lymphocytosis, increased CSF interferon-alpha and negative serological investigations for common prenatal
infections. Aicardi and Goutières (1984) first reported eight cases in five families beginning in infancy, with calcification of the basal ganglia and chronic CSF lymphocytosis, leading rapidly to a vegetative state and early death. Lebon et al. (1988) described the intrathecal synthesis of interferon-alpha in patients with AGS which is also elevated in viral CNS infections and autoimmune disorders like systemic lupus erythematosus, suggesting a common pathogenic mechanism. Interferon-alpha may have a pathogenic role in AGS as indicated by the observation that astrocyte-specific chronic overproduction of interferon-alpha in transgenic mice recapitulates the neuropathological findings seen in AGS (Akwa et al. 1998).

The classic phenotype includes a very early onset in the first weeks or months of life so that deterioration, if any, is far from obvious. The clinical picture resembles an in utero viral infection. The general condition of the patient is poor. There is marked hypotonia interrupted by opisthotonic episodes, failure to develop, febrile episodes, and death in a state of decerebration within a few years, although some children survive for several years (Aicardi and Goutières 1984; Goutières et al. 1998). The two major diagnostic features are: (1) the presence of calcification of the basal nuclei, sometimes also of the periventricular white matter and the dentate nuclei, associated with hypodensities of the white matter and brain atrophy (Fig. 10.8); and (2) a persistent mild CSF lymphocytosis (10–80 cells per mm$^3$) that is not constant and tends to decrease with time. Outside the nervous system, thrombocytopenia, hepatosplenomegaly and elevated hepatic transaminases along with intermittent fever may also erroneously suggest an infective process. Cutaneous lesions (chilblain-like) are present in about half the cases. Moderately elevated levels of interferon-alpha are present in CSF in most cases, at least in the first years of the disease (Lebon et al. 1988) and to a lesser extent in the blood. Similar cases have been reported as 'Cree encephalitis' from highly inbred Indian communities of Northern Quebec (Black et al. 1988).

Beside this classic form, a wide phenotypic spectrum has been recognised and most of the original criteria for diagnosis no longer apply: affected individuals may show later onset and may not have severe or progressive neurological dysfunction, calcification of the basal ganglia, or CSF lymphocytosis. The appearance of chilblains is an important clinical sign for correct diagnosis (see Stephenson 2008 for a review).

AGS is a genetically heterogeneous syndrome. To date seven different forms (AGS1–7; see Table 10.5) caused by mutations in different genes have been described with both recessive and dominant – with variable penetrance – inheritance patterns. AGS1 (MIM #225750) is caused by homozygous or compound heterozygous mutations in the \textit{TREX1} gene encoding a nuclear protein with 3’ exonuclease activity involved in DNA repair on chromosome 3p21 (Crow et al. 2006a). Cree encephalitis has been found to be allelic of AGS1. AGS1 has also been reported to be caused by heterozygous mutations in this gene (Haaxma et al. 2010). The same mutation in heterozygosity had previously been identified by Lee-Kirsch et al. (2007) in a family with chilblain lupus. AGS2 (MIM #610181) is

![Figure 10.8](image)

**Figure 10.8** Leukodystrophy with calcification of the basal ganglia (Aicardi–Goutières syndrome). (a) Axial MRI scan showing punctate calcification in the basal ganglia, low signal from the frontal lobes, and diffuse moderate atrophy of the brain. Note the presence of calcification in the white matter. (b) MRI scan of the basal ganglia: punctate calcifications are well shown as low-intensity signals.

<table>
<thead>
<tr>
<th>Name</th>
<th>MIM no.</th>
<th>Mode of inheritance</th>
<th>Gene (chromosome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGS1</td>
<td>#225750</td>
<td>AR/AD</td>
<td>\textit{TREX1} (3p21)</td>
</tr>
<tr>
<td>AGS2</td>
<td>#610181</td>
<td>AR</td>
<td>\textit{RNASEH2B} (13q14)</td>
</tr>
<tr>
<td>AGS3</td>
<td>#610329</td>
<td>AR</td>
<td>\textit{RNASEH2C} (11q13.1)</td>
</tr>
<tr>
<td>AGS4</td>
<td>#610333</td>
<td>AR</td>
<td>\textit{RNASEH2A} (19p13.2)</td>
</tr>
<tr>
<td>AGS5</td>
<td>#612952</td>
<td>AR</td>
<td>\textit{SAMHD1} (20q11.2)</td>
</tr>
<tr>
<td>AGS6</td>
<td>#615010</td>
<td>AR/AD</td>
<td>\textit{ADAR} (1q21.3)</td>
</tr>
<tr>
<td>AGS7</td>
<td>#615846</td>
<td>AD</td>
<td>\textit{IFIH1} (2q24.2)</td>
</tr>
</tbody>
</table>

AGS, Aicardi–Goutières syndrome; AR, autosomal recessive; AD, autosomal dominant.
caused by homozygous or compound heterozygous mutations in the \textit{RNASEH2B} gene encoding the non-catalytic subunit B of ribonuclease H2 involved in DNA replication on chromosome 13q14 (Ali et al. 2006; Crow et al. 2006b). AGS3 (MIM \#610329) is caused by homozygous mutations in the \textit{RNASEH2C} gene encoding the non-catalytic subunit C of ribonuclease H2 on chromosome 11q13.1 (Crow et al. 2006a). AGS4 (MIM \#610333) is caused by homozygous or compound heterozygous mutations in the \textit{RNASEH2A} gene encoding the catalytic subunit A of ribonuclease H2 on chromosome 19p13.2 (Crow et al. 2006b); AGS5 (MIM \#612952) is caused by homozygous or compound heterozygous mutations in the \textit{SAMHD1} gene encoding a protein involved in the immune response to viral infection on chromosome 20q11.2 (Rice et al. 2009); AGS6 (MIM \#615010) can be caused by homozygous, compound heterozygous or heterozygous mutations in the \textit{ADAR} gene encoding an enzyme involved in RNA editing on chromosome 1q21.3 (Rice et al. 2012). AGS7 (MIM \#615846) is caused by heterozygous mutations in the \textit{IFIH1} gene coding for a putative RNA helicase on chromosome 2q24.2 (Rice et al. 2014).

Rice et al. (2007) analysed clinical data from 123 mutation-positive patients. Two clinical presentations could be delineated: a more severe early-onset neonatal form, with high mortality, highly reminiscent of congenital infections seen particularly with \textit{TREX1} mutations, and a milder, later onset presentation, sometimes occurring after several months of normal development and associated with low mortality and occasionally with remarkably preserved neurological function, most frequently due to \textit{RNASEH2B} mutations. Further genotype–phenotype correlations are yet to be established.

**CEREBRORETINAL MICROANGIOPATHY WITH CALCIFICATIONS AND CYSTS**

**Coats Plus Syndrome**

Cerebroretinal microangiopathy with calcifications and cysts (CRMCC; MIM \#612199), also known as Coats plus syndrome, is an autosomal recessive infantile or early childhood onset disorder characterised by progressive extensive intracranial calcifications, leukodystrophy, and brain cysts, resulting in ataxia, spasticity, dystonia, seizures, and variable cognitive decline. Patients also have bilateral retinal telangiectasias and exudates (Coats disease) as well as extra-neurological manifestations, including poor growth, hair, skin and nail changes, gastrointestinal telangiectasias with risk of haemorrhage, skeletal abnormalities with osteopenia and sclerosis with increased fractures, and bone marrow suppression with anaemia and thrombocytopenia. A primary obliterator cerebral angiopathy involving small vessels, leading to calcifications, slow necrosis, cyst formation, and secondary white matter abnormalities has been postulated. Brain MRI showing progressive intracerebral calcifications involving deep grey nuclei, brainstem, cerebral and cerebellar white matter, and dentate nuclei, accompanied by diffuse white matter signal abnormality. About 30 cases have been reported to date. CRMCC is caused by compound heterozygous mutations in the \textit{CTC1} gene encoding a component of the CST complex, involved in the protection of telomeres from degradation, on chromosome 17p13 (Anderson et al. 2012; Polvi et al. 2012).

Another disorder called leukoencephalopathy, brain calcifications, and cysts (LCC; MIM \#614561), also known as Labrune syndrome (Labrune et al. 1996; see Other Demyelinating/Dysmyelinating Leukodystrophies section), has similar neurological features to CRMCC in the absence of extra-neurological manifestations. However, mutations in the \textit{CTC1} gene have not been found in patients with Labrune syndrome, suggesting that the two disorders are not allelic (Anderson et al. 2012; Polvi et al. 2012).

**SJÖGREN-LARSSON SYNDROME**

**Fatty Aldehyde Dehydrogenase Deficiency**

Sjögren-Larsson syndrome (SLS; MIM \#270200) is an autosomal recessive, early childhood onset disorder caused by an inborn error of lipid metabolism and characterised by congenital ichthyosis, intellectual disability, spasticity, macular dys trophy and leukoencephalopathy (for review see Fuijkschot et al. 2012). It is caused by homozygous or compound heterozygous mutations in the \textit{ALDH3A2} gene, which encodes fatty aldehyde dehydrogenase (FALDH), an enzyme that catalyses the oxidation of fatty aldehydes to fatty acids, on chromosome 17p11. Prevalence is estimated at 1/250 000 worldwide, but the syndrome is more common in Sweden due to a founder effect (Jagell et al. 1981).

Mild to moderate ichthyosis is usually present at birth and progresses during infancy. Neurological signs appear during infancy and consist of spastic diplegia or, less frequently, spastic tetraplegia. Approximately one-half of patients are non-ambulatory. Seizures occur in about 40% of cases. Intellectual disability varies from mild to severe, although rare patients with normal intellect have been reported. Ophthalmological involvement is often present and is characterised by retinal crystalline inclusions (so-called glistening white dots) surrounding the fovea. Brain MRI showing hypomyelination and a variable degree of periventricular dysmyelination and ventricular enlargement, and 1H-MR-spectroscopy reveals a characteristic abnormal lipid peak in periventricular white matter (van Domburg et al. 1999). In early infancy, before the onset of spasticity, differential diagnosis includes other forms of congenital ichthyosis. Once neurological symptoms appear later in infancy, differential diagnosis includes other neuro-ichthyotic syndromes such as neutral lipid storage disease (Chanarin-Dorfman syndrome), multiple sulphatase deficiency and Refsum disease.

SLS is diagnosed by measuring FALDH or fatty alcohol oxidoreductase (FAO) activity in cultured fibroblasts from skin biopsies. Identification of abnormal urinary excretion of leukotriene B4 and its metabolites may also be useful. Diagnosis can be confirmed by demonstration of \textit{ALDH3A2}
gene mutations. Prenatal diagnosis is possible, by measuring the conversion of phytol into phytanic acid in chorionic villus biopsy samples, or by mutation analysis of the sample. Treatment should be multidisciplinary including neurologists, dermatologists, ophthalmologists, orthopaedic surgeons and physiotherapists. Limited clinical improvement has been shown using special diets with reduced fatty intake and supplementation with both n-3 and n-6 fatty acids to obtain a linoleic/linolenic acid ratio of 6, when tried early in the disease. Therapeutic trials with zileuton, a 5-lipoxygenase inhibitor and gene therapy are being tried.

CEREBROTENDINOUS XANTHOMATOSIS

Van Bogaert-Scherer-Epstein Disease

Cerebrotendinous xanthomatosis (CTX; MIM #213700) is an inherited lipid storage disease caused by homozygous or compound heterozygous mutations in the CYP27A1 gene coding for the bile acid biosynthetic enzyme sterol 27-hydroxylase on chromosome 2q35. Clinically it is characterised by beginning in late childhood or early adolescence with progressive neurological dysfunction including cerebellar ataxia, spinal cord involvement and cognitive decline, tendon xanthomas, premature atherosclerosis and cataracts. The presence of chronic diarrhoea and a history of prolonged neonatal cholestatic jaundice support the diagnosis (Mignatti et al. 2014). Large deposits of cholesterol and cholestanol are found in virtually every tissue, particularly the Achilles tendons, brain and lungs. The diagnosis can be made by demonstrating high serum levels of cholestanol. Dotti et al. (1994) described the CT and MRI findings in brain and spinal cord of ten patients aged 35 years or older with cerebrotendinous xanthomatosis. All of them had cerebral and/or cerebellar atrophy, and the majority had focal lesions distributed through the brain, cerebellum, brainstem or basal nuclei. More recently, Lionnet et al. (2014) described the clinical and paraclinical findings in 15 adult patients, with 73% beginning in childhood. Brain MRI was abnormal in all cases and showed images of periventricular leukodystrophy in 73% with predominant posterior brain involvement in 60%, T2-weighted hyperintensity of the dentate nuclei in 47%, hyperintensity of the cortico-spinal tracts in 53% and cerebral atrophy in 33%. Oral therapy with chenodeoxycholic acid has been shown to arrest the progression of the disease but not to reverse the clinical manifestations. Thus early diagnosis is essential.

L-2-HYDROXYGLUTARIC ACIDURIA

L-2-hydroxyglutaric aciduria (MIM #236792) is an autosomal recessive early childhood onset neurological disorder caused by homozygous mutations in the L2HGDH gene encoding L-2-hydroxyglutarate dehydrogenase, a FAD-dependent mitochondrial enzyme that oxidises L-2-hydroxyglutarate to alphaketoglutarate, on chromosome 14q21 (Rzem et al. 2004; Topçu et al. 2004). About 150 cases have been reported to date. Clinical onset is often insidious in the first year of life. Presenting symptoms include psychomotor retardation and epilepsy. The disease slowly progresses, with cognitive decline, spasticity and cerebellar and extrapyramidal signs leading to loss of independent walking. Most reported patients had macrocephaly. An increased incidence of brain tumours has been reported (Aghili et al. 2009). Brain MRI showing subcortical white matter signal abnormalities, cerebellar atrophy, and signal changes in the putamina and dentate nuclei. Urinary organic acid screening reveals a massive increase of 2-hydroxyglutaric acid, and subsequent chiral differentiation is needed to establish the biochemical diagnosis of L-2-hydroxyglutaric aciduria. Demonstration of L2HGDH gene mutations allows diagnostic confirmation. Prenatal diagnosis can be performed by mutational analysis and by the measurement of L-2-hydroxyglutaric acid in amniotic fluid. No specific treatment exists. Prognosis is poor but most patients reach adulthood.

OTHER DEMYELINATING/DYSMYELINATING LEUKODYSTROPHIES

Leukodystrophy with palmo-plantar keratoderma is an autosomal recessive disorder described by Lossos et al. (1995) in four siblings with early childhood onset palmpoplantar keratoderma followed in adulthood by a progressive tetrapyrimald syndrome and cognitive impairment. Investigation disclosed cerebral white matter involvement on MRI and an arylsulphatase A pseudodeficiency carrier state, which was also identified in clinically unaffected family members. The skin content of collagen and total protein was higher in the affected patients. The authors suggested that an extracellular matrix abnormality may be involved in the pathogenesis of this disorder. Further cases have not been reported to date.

Skin abnormalities were also present in dermatoleukodystrophy (MIM #221790) described by Matsuyama et al. (1978) in a Japanese brother and sister born with thickened wrinkled skin resulting in a progeroid appearance who died in the third year of life from a progressive cerebral disease with cognitive and motor impairment. Postmortem neuropathologic studies showed a leukodystrophy with multiple axonal spheroids. Ultrastructurally, the spheroids contained granules resembling ceroid-lipofuscin bodies. Similar granules were found in degenerating oligodendrocytes and in Schwann cells. The skin showed hypercellularity and sclerosis. Further cases have not been reported to date.

A rare type of prenatal autosomal recessive leukodystrophy known as the Wiedeman–Rautenstrauch syndrome or neonatal progeroid syndrome (MIM #264090) has been reported, with progeroid features in association with demyelination of early onset (Martin et al. 1984). About 30 cases have been reported to date.

Cutaneous angiomatosis and pigmentation abnormalities were described in rare cases of familial non-calcifying
cortico-meningeal angiomatosis with progressive demyelination reported by Divry and Van Bogaert (1946).

A diffuse cerebral microangiopathy is thought to be responsible for diffuse dymyelination, calcification in brain and cerebellum and cyst formation resulting in spasticity, dystonia, seizures and cognitive decline in three unrelated children reported by Labrune et al. (1996) (Fig 10.9). The Labrune syndrome, also known as leukoencephalopathy, brain calcifications and cysts (LCC; MIM #614561), has similar features to ‘Coats plus syndrome’ or cereboretinal microangiopathy with calcifications and cysts [CRMCC; MIM #612199; see Cereboretinal Microangiopathy with Calcifications and Cysts (Coats Plus Syndrome) section above] in the absence of extra-neurological manifestations.

**Leukoencephalopathy with metaphyseal chondrodysplasia** (LKMCD; MIM #300660) has been described by Neubauer et al. (2006) in four males of a three-generation German family with childhood onset slowly progressive leukoencephalopathy with tremor, ataxia, optic atrophy and spastic tetraparesis, associated with metaphyseal chondrodysplasia with broad wrists and knees. Brain MRI showed diffuse cerebral demyelination. Radiography showed areas of marked radiolucency in the distal metaphyses of radius and cubitus. Brain MRI showed areas of marked demyelination in the distal metaphyses of radius and cubitus. Brain MRI showed areas of marked demyelination in the distal metaphyses of radius and cubitus. Postmortem examination of one case showed cerebral atrophy, a hypoplastic corpus callosum, thin optic nerves, and atrophic pyramidal tracts. Astrocytes were markedly increased. Bone mineralisation was diffusely decreased. Inheritance was consistent with an X-linked recessive pattern and linkage analysis of the X chromosome identified a 14-cM candidate region on Xq25-q27.

**Progressive cavitating leukoencephalopathy** was clinically characterised by Naidu et al. (2005) in 19 patients from 16 families with a neurodegenerative syndrome characterised by acute onset of irritability or neurological deficits between 2 months and 3.5 years of age, followed by steady or intermittent clinical deterioration leading to generalised spasticity, dementia, vegetative state and death in childhood or early adolescence, and patchy leukoencephalopathy with cavities, and vascular permeability in actively affected regions on brain MRI. Early lesions affected corpus callosum and centrum semiovale, with or without cerebellar or cord involvement, and after repeated episodes, lesions coalesced resulting in large cystic regions in brain or spinal cord. Grey matter was spared until late in the course. Partial clinical or MRI recovery may occur after episodes. Elevated levels of lactate in brain, blood and CSF, abnormal urine organic acids and changes in muscle respiratory chain enzymes were present. Pathological studies showed severe loss of myelin sparing U-fibres, axonal disruption, and cavitary lesions without inflammation. Familial occurrence and consanguinity suggested autosomal recessive inheritance. Ferreira et al. (2011) reported two siblings with progressive cavitating leukoencephalopathy associated with respiratory chain complex I deficiency and a novel mutation in NADH dehydrogenase (ubiquinone) Fe-S protein 1 (NDUFS1) gene, encoding the largest subunit of complex I, on chromosome 22q33-q34.

Other hereditary disorders, both autosomal recessive such as the adult polyglucosan body disease (MIM #263570) and dominant such as the autosomal dominant adult-onset demyelinating leukodystrophy (ADLD; MIM #169500) and the hereditary diffuse leukoencephalopathy with spheroids (HDLS; MIM #221820) cause progressive nervous system involvement with demyelination/dysmyelination but with adult-onset so they will not be discussed in detail in this chapter. Only one case of HDLS, also known as van Bogaert–Nyssen disease, hereditary diffuse leukoencephalopathy with axonal spheroids and pigmented glia or pigmented type of orthochromatic leukodystrophy, with childhood onset has been reported (Seiser et al. 1990).

**HYPOMYELINATING LEUKODYSTROPHIES**

The term hypomyelinating leukodystrophies (Schiffmann et al. 1994; Schiffmann and van der Knaap 2009) refers to inherited white matter disorders in which abnormalities in myelin development occur rather than destruction. The paucity of myelin development due to several genetic causes is thus the primary feature in hypomyelinating leukodystrophies. However, we will also include in this chapter some inherited white matter disorders with hypomyelination, in which the hypomyelination is thought to be secondary to neuronal disease, such as hypomyelinating leukodystrophy-3 (HLD3; MIM #260600), mitochondrial HSP60 chaperonopathy or hypomyelinating leukodystrophy-4 (HLD4; MIM #612233) and global cerebral hypomyelination or AGC1 deficiency (MIM #612949). In these cases, besides hypomyelination there are often prominent signs of grey matter involvement, such as early and severe brain atrophy with microcephaly, early-onset epilepsy and severe intellectual disability. Advances in genetics have led to the delineation of many of these disorders in recent years. Nonetheless, almost half of the patients with hypomyelination remain without genetic diagnosis. Most of these disorders have no specific treatment at present.

![Figure 10.9 Pelizaeus–Merzbacher disease. T2-weighted image showing moderately increased signal from the periventricular white matter.](image)
However, emerging research in oligodendrocyte biology and neuroradiology may result in the possibility of clinical trials of both pharmacological and cell-based therapies in the near future (Pouwels et al. 2014).

PELIZAEUS–MERZBACHER DISEASE

Pelizaeus–Merzbacher disease (PMD; MIM #312080) is an X-linked recessive hypomyelinating leukodystrophy (HLD1) in which myelin is not formed properly in the CNS, clinically characterised by early developmental impairment, nystagmus, hypotonia, choreoathetosis, and later on ataxia and spasticity. The classic form of PMD was first described by Pelizaeus (1885). Merzbacher (1910) described the neuropathology of the original family examined by Pelizaeus and conceived the disorder to be the result of a congenital aplasia of myelin sheaths. Much later biochemical analysis of cerebral white matter revealed a pattern consistent with that found in fetal myelin including a reduction of the proteolipid protein (PLP). Seitelberger added a congenital variant (type II). According to severity a transitional type III has also been defined.

The neuropathology of classic PMD (type I) is described as patchy hypo- and dysmyelination (so-called tigroid pattern), whereas type II exhibits almost total absence of myelin (Seitelberger 1995).

Deletions, duplications and mutations of the PLP1 gene on chromosome Xq22 give rise to the disorder. Duplications of the PLP1 gene, found in up to 60% of cases, are the major cause of PMD, whereas point mutations are less frequent (Sistemans et al. 1998). PLP1 codes additionally for DM20, another protein in the CNS.

Wolf et al. (2005) reported five unrelated patients with an atypically severe form of PMD who had three, and in one case, five copies of the PLP1 gene demonstrating that severe clinical symptoms are associated with increased PLP1 gene dosage. Regis et al. (2008) found no association between clinical disease severity and the extent of the duplicated segment among five unrelated PMD patients with PLP1 duplications.

Spastic paraplegia-2 (SPG2; MIM #312920) is an allelic disorder, and there is a clinical continuum between SPG2 and the milder forms of PMD.

Clinical and radiological criteria for the diagnosis of the classic form of PMD have been published (Bouloche and Aicardi 1986). They include the occurrence in a male patient of delayed motor development before 3 years of age (most often from a few months of age) and ophthalmological and neurological signs. Nystagmus is often the first detected manifestation. Hypotonia, choreoathetosis, and later on ataxia and spasticity develop progressively. Most patients show slow improvement until the age of 10–12 years. The majority of patients learn to sit; some are able to walk with aid but rarely independently. A minority develop active language. Most patients reach a plateau in development followed by a slow regression with dystonia, increasing ataxia, spasticity and the development of optic atrophy.

The congenital type II (Haenggeli et al. 1989) showing a more severe course with limited development before deterioration, even though its onset may not be much earlier than in the classic type. The five patients described by Wolf et al. (2005) developed severe symptoms before the age of 3 months with hypotonia, nystagmus, stridor and seizures. Two died at 7 and 9 months respectively; three suffered from severe epilepsy.

An array of clinical, electrophysiological and neuroradiological signs leads to the diagnosis. Early developmental impairment, nystagmus, muscular hypotonia and choreiform movements are characteristic clinical symptoms. Nystagmus may disappear before the age of 2 years. Disturbance of cerebral conduction of auditory and/or visual evoked potentials and a diffuse hyperintensity of the white matter on T2-weighted MRI are almost diagnostic for PMD. In the classic form an arrest of myelination in an early stage of development is shown in combination with progressive abnormalities of the unmyelinated white matter and possibly a slow degradation of some myelin. In the connatal form a complete absence of myelin in the brain is demonstrated (van der Knaap and Valk 1989). High signal intensity is seen in all unmyelinated white matter structures on T2-weighted images (Fig. 10.10), and low signal intensity on T1-weighted images. However, CT may be normal or show only some atrophy. MRS reveals a metabolic pattern of white matter similar to grey matter with increased concentrations of NAA, glutamine, myo-inositol, creatine and phosphocreatine, while the concentration of the choline-containing component is reduced. The proton MRS profile of PMD therefore differs from the pattern commonly observed in other leukodystrophies (Hanefeld et al. 2005).

To date, only symptomatic treatment is available for PMD. However, a phase I clinical study of allogenic neural stem cells transplantation in four patients with congenital PMD have showed the safety of the procedure and MRI changes in the region of the transplant suggestive of engraftment and consistent with the possibility of myelin formation, and encourages later phase II/III testing to prove efficacy of this approach (Gupta et al. 2012).

Pelizaeus–Merzbacher-Like Disease

The PMD phenotype has frequently been observed in patients without mutations or duplications of the PLP1 gene and these cases were classified as PMD-like disease (PMLD).

Uhlenberg et al. (2004) studied six families with PMLD, and in one Turkish consanguineous family and two German nonconsanguineous families, they identified five different mutations in the GJC2/GJA12 gene, encoding the gap junction protein alpha 12 (connexin 46.6), on chromosome 1q41. In the other three affected families, no GJC2/GJA12 mutations were found, suggesting that other atypical forms with a similar clinical presentation probably belong to other disorders. PMLD due to GJC2/GJA12 mutations, also known as PMLD1 or HLD2 (MIM #608804), is inherited as an autosomal recessive trait and, in addition to the PMD-like clinical picture, the patients also show signs of a peripheral
neuropathy and sporadic seizures. Henneke et al. (2008) identified \( GJA12 \) mutations in only 7.7% of 182 families with a PMD-like phenotype, and concluded that \( GJA12 \) mutations are a rare cause for a PMD-like disorder.

Feinstein et al. (2010) reported seven individuals from an extended consanguineous Israeli Bedouin kindred with an autosomal recessive form of connatal Pelizaeus–Merzbacher disease due to a homozygous mutation in the \( AIMPI \) gene, encoding a cytokine involved in inflammatory processes, on chromosome 4q24. This form has been called hypomyelinating leukodystrophy-3 (HLD3; MIM #260600). However, Boespflug-Tanguy et al. (2011) replied that the patients described by Feinstein et al. did not present the core clinical and neuroradiological symptoms that define a hypomyelinating leukodystrophy, corresponding to a primary CNS myelin formation defect, but with features of white matter involvement secondary to neuronal involvement, and consequently should not be considered as a PMLD.

Magen et al. (2008) reported a large consanguineous Israeli Bedouin family with an autosomal recessive form of severe hypomyelinating leukoencephalopathy due to a mutation in the \( HSPD1 \) gene, encoding a mitochondrial chaperonin, on chromosome 2q33.1. There was a range of phenotypic heterogeneity, with onset between birth and age 3 months and death within the first two decades of life. Patients with more severe forms suffered from apneic spells during acute febrile illnesses and died before the age of 2 years. Patients who survived beyond the age of 2 years developed progressive limb spasticity and contractures. Plasma lactate levels were sometimes increased during encephalopathic episodes but there was no evidence of ragged red fibres on muscle biopsies. MRI showed no evidence of normal myelination and in more severe cases some degree of atrophy of cortex and brainstem. This disorder due to mutations in the \( HSPD1 \) gene has been called mitochondrial HSP60 chaperonopathy, MitCHAP60 disease or hypomyelinating leukodystrophy-4 (HLD4; MIM #612233), although signs of prominent grey matter involvement are present. Autosomal dominant hereditary spastic paraplegia-13 (SPG13; MIM #605280) is an allelic disorder.

**Hypomyelination and Congenital Cataracts**

Hypomyelinating leukodystrophy-5 (HLD5), also known as hypomyelination and congenital cataracts (HCC; MIM #610532), is caused by a homozygous mutation in the \( FAM126A \) gene, coding the membrane protein hyccin, on chromosome 7p15.3 (Zara et al. 2006).

Clinically HCC/HLD5 is characterised by cataracts mostly at birth or in the first 2 months of life, developmental delay by the end of the first year of life, with delayed standing and walking, and later on slowly progressive pyramidal and cerebellar dysfunction, and mild to moderate intellectual disability. Brain MRI showing diffuse cerebral hypomyelination. There is often peripheral nervous system involvement with a sensorimotor demyelinating neuropathy. Some patients have seizures. There is a certain clinical variability as some patients may have a somewhat milder disease course, with onset of cataracts in infancy or later and some ability to walk in childhood (Ugur and Tolun 2008; Biancheri et al. 2011).

**Hypomyelination with Atrophy of Basal Ganglia and Cerebellum**

Hypomyelinating leukodystrophy-6 (HLD6), also known as hypomyelination with atrophy of basal ganglia and cerebellum (HABC; MIM #612438), is caused by mutations in the \( TUBB4A \) gene, encoding a beta tubulin family involved in the formation of microtubules, on chromosome 19p13.

It was first described by van der Knaap et al. (2002b) in seven unrelated patients with neurological impairment associated with a distinct brain MRI pattern characterised by hypomyelination and atrophy of the basal ganglia and cerebellum that develop over time. Clinical features included onset at 1–3 years of delayed motor development, with difficulty or absent walking and later deterioration of motor skills with spasticity and extrapyramidal signs such as rigidity, dystonia and choreoathetosis. Most patients showed mild intellectual disability. Two patients were more severely affected with onset at age 2 months, poor vision with optic atrophy, poor motor development, seizures and intellectual disability. Brain MRI showed a homogeneous picture, with diffuse myelin deficiency, atrophy of the cerebellar vermis, and small or absent putamen, with variable progression in serial studies.

HABC/HLD6 is mostly due to de novo heterozygous mutations and occurs sporadically. Two sibs with the disorder, however, have been reported who inherited the mutation from their unaffected mother, who was found to be somatic-mosaic for the mutation (Simons et al. 2013).
POLYMERASE III-RELATED HYPOMYELINATING LEUKODYSTROPHIES

In recent years, mutations in genes coding for the RNA polymerase III (Pol III) subunits POLR3A and POLR3B have been shown to be a major cause of childhood-onset hypomyelinating leukodystrophies with prominent cerebellar dysfunction, oligodontia, and hypogonadotropic hypogonadism. POLR3A is the largest of the 17 subunits that constitute Pol III. It forms, together with POLR3B, the second largest subunit, the catalytic centre of the enzyme. Pol III transcribes small untranslated RNAs involved in the regulation of essential cellular processes, including transcription, RNA processing, and translation. These conditions have been referred to as Pol III-related hypomyelinating leukodystrophies, and it has been suggested that mutations in genes coding for other Pol III subunits, and possibly in genes coding for proteins interacting with Pol III, could be responsible for cases of genetically uncharacterised hypomyelinating leukodystrophies (Tétreault et al. 2011).

HYPOMYELINATING LEUKODYSTROPHY 7 WITH OR WITHOUT OLIGODONTIA AND/OR HYPOGONADOTROPIC HYPOGONADISM

Bernard et al. (2011) demonstrated that the majority of previously reported cases affected by tremor-ataxia with central hypomyelination (TACH), hypomyelination, hypodontia and hypogonadotropic hypogonadism (4H syndrome) and leukodystrophy with oligodontia were caused by homozygous or compound heterozygous mutations in the POLR3A gene on chromosome 10q22.3.

Also called hypomyelinating leukoencephalopathy with ataxia and delayed dentition; ataxia, delayed dentition and hypomyelination (ADDH); hypomyelinating leukoencephalopathy with hypodontia and hypogonadotropic hypogonadism (4H syndrome), the hypomyelinating leukodystrophy 7 (HLD7; MIM #607694) is clinically characterised by childhood onset of progressive motor decline with prominent cerebellar signs combined with a variable degree of pyramidal signs that may seem to be almost stable for several years. There is mild intellectual disability and/or slowly progressive cognitive decline. High-level myopia has been reported in some patients. Other features may include hypodontia or oligodontia and hypogonadotropic hypogonadism. Brain MRI showing diffuse hypomyelination, cerebellar atrophy and a thin corpus callosum.

To date about 30 patients have been reported. Clinical variability has been demonstrated. Timmons et al. (2006) reported four unrelated patients with delayed tooth eruption and hypodontia of permanent teeth, otherwise asymptomatic until age 7 (in one case) or 12 years (in three cases), when progressive hypomyelination and dysmyelination resulted in ataxia, dysmetria, spasticity, dysarthria and mild cognitive impairment. All four had hypogonadotropic hypogonadism. Sural nerve biopsy showed loss of normal myelin periodicity. However, peripheral nerve abnormalities have not been further reported. On the other hand, Bernard et al. (2010) reported seven patients from five families with a similar form in very early childhood, with average age at onset of 2.5 years, becoming wheelchair-bound by later childhood. Only two of seven patients had hypodontia, one had hypogonadotropic hypogonadism and none had peripheral nerve abnormalities.

HYPOMYELINATING LEUKODYSTROPHY 8 WITH OR WITHOUT OLIGODONTIA AND/OR HYPOGONADOTROPIC HYPOGONADISM

Saitsu et al. (2011) and Tétreault et al. (2011) found compound heterozygous mutations in the POLR3B gene on chromosome 12q23 respectively in three patients from two unrelated nonconsanguineous Japanese families and in three unrelated European patients who had a phenotype consistent with 4H syndrome but who did not have mutations in the POLR3A gene.

This entity has been called hypomyelinating leukodystrophy 8 (HLD8; MIM #614381) and clinically is similar to HLD7. About 15 cases have been reported to date (Saitsu et al. 2011; Daoud et al. 2013). In the MRI, though, both HLD7 and HLD8 show diffuse hypomyelination, cerebellar atrophy and a thin corpus callosum. Takanashi et al. (2014) have recently described different MRI patterns: patients with POLR3B mutations show smaller cerebellar structures, especially vermis, and milder hypomyelination than those in POLR3A mutations.

ALLAN-HERNDON-DUDLEY SYNDROME

Allan-Herndon-Dudley syndrome (AHDS; MIM # 300523), also known as monocarboxylate transporter 8 deficiency, triiodothyronine (T3) resistance or X-linked intellectual disability with hypotonia, is caused by mutations in the SLC16A2 gene on chromosome Xq13, encoding the monocarboxylate transporter-8, a protein involved in the cellular importation of thyroid hormone.

The first clinical description was made by Allan et al. (1944) in 24 males in six generations of a family. Affected males had hypotonia from birth, severe motor developmental delay and generalised muscular atrophy, joint contractures and hyporeflexia as adults. Stevenson et al. (1990) restudied the same family with five additional affected males in two generations, and completed the phenotypic description by reporting severe intellectual disability, dysarthria, ataxia, athetoid movements, generalised weakness with muscular atrophy, long face with bitemporal narrowing large, simple ears, and spastic paraplegia with hyper-reflexia, clonus, Babinski reflexes and joint contractures. An X-linked recessive pattern of inheritance was suggested.
Dumitrescu et al. (2004) found mutations in the SLC16A2 gene in two unrelated families in which males showed the typical clinical picture of AHDS. Rotatory nystagmus, impaired gaze and hearing loss were also reported. Serum thyroxine (T4) was decreased, TSH was normal to mildly increased, and serum T3 was increased. Free T4 was also decreased or at the lower limits of normal. Heterozygous females had a milder thyroid phenotype without neurological deficits.

Vaurs-Barriere et al. (2009) identified mutations in the SLC16A2 gene in 11% of 53 families in which a male was affected with a hypomyelinating leukodystrophy with a Pelizaeus–Merzbacher-like phenotype of unknown aetiology. MRI showed hypomyelination affecting early myelinated areas before age 2 years, although, unlike PMD, it appeared to improve with age, without associated neurological deterioration. The authors concluded that males with a Pelizaeus–Merzbacher-like phenotype should be screened for SLC16A2 mutations.

**18q–SYNDROME**

18q-syndrome (MIM #601808) is an autosomal dominant disorder caused by a terminal macrodeletion on chromosome 18q23 that includes the MBP gene, coding for the myelin basic protein, a major constituent of the myelin sheath formed by oligodendrocytes and Schwann cells in the nervous system. Direct transmission of the deletion from mother to child has been reported. Hence, affected females, being fertile, should have genetic counselling (Chen et al. 2006). The clinical presentation is variable including generalised dysmorphic signs like microcephaly, high or cleft palate, narrow ear canals, clinodactyly, congenital heart disease and short stature. Cognitive retardation may be combined with hypotonia, choreoathetosis, poor coordination, nystagmus and seizures. Behavioural problems can be prominent. MRI showing diffuse hyperintensity throughout the cerebral white matter in T2-weighted images consistent with hypomyelination (Linnankivi et al. 2006). Interestingly, a recent study with MRS has shown increased concentrations of creatine, myo-inositol and choline with a normal N-acetylaspartate one, suggesting reactive astrocytic gliosis and accelerated myelin turnover as the cause of white matter abnormalities in 18q syndrome (Tada and Takanashi 2014), which is consistent with recent pathological reports (Tanaka et al. 2012).

**OCULODENTODIGITAL DYSPLASIA**

Autosomal dominant oculodentodigital dysplasia (ODDD; MIM #164200) is caused by heterozygous mutation in the gap junction protein alpha 1 (GJA1) or connexin-43 gene on chromosome 6q22.31. Clinically it is characterised by facial dysmorphism and variable involvement of the eyes, dentition and fingers. Characteristic facial features include a narrow, pinched nose with hypoplastic alae nasi, prominent columella and thin anteverted nares together with a narrow nasal bridge, and prominent epicantthic folds giving the impression of hypertelorism. Eye findings include microphthalmia and microcornea. The teeth are usually small and carious. The characteristic digital malformation is complete syndactyly of the fourth and fifth fingers. Associated lymphedema has also been reported. Neurological features include progressive spasticity, bladder and bowel dysfunction, visual and hearing loss, ataxia and nystagmus. Cognitive impairment has been described in some patients. Diffuse, abnormally high signal intensity in T2-weighted images in the subcortical white matter bilaterally, as well as basal ganglia changes, are seen on MRI (Loddenkemper et al. 2002).

A rare and more severe autosomal recessive form of ODDD (MIM #257850) is also caused by mutations in the GJA1 gene (Richardson et al. 2006).

**FREE SIALIC ACID STORAGE DISORDERS AND SALLA DISEASE**

Free sialic acid storage diseases are autosomal recessive lysosomal storage diseases that may present as a severe infantile form (infantile sialic acid storage disease, ISSD) or as a slowly progressive form that is prevalent in Finland (Salla disease).

Salla disease (SD; MIM #604369), also known as Finnish type of sialuria, was first described in Finland by Aula et al. (1979). The name Salla refers to the birthplace of the first described patients. The efflux of sialic acid from lysosomes is disturbed by a transporter defect. The related gene SLC17A5 (also called AST, acidic sugar transporter) is located on chromosome 6q13 (Haataja et al. 1994).

Symptoms appear at 6–18 months of age in the form of hypotonia, ataxia, athetosis and transient nystagmus. Later, slow progression occurs and spastic symptoms, growth retardation and dysmorphic, gargoyle-like features develop. However, most patients reach adulthood. Cognitive development and speech are affected, most patients using only single words or short sentences. An unusually severe form of Salla disease has been described by Haataja et al. (1994); patients were had severe intellectual disability, either not responsive to the environment or responding only with facial gestures. Milder variants and single patients living outside Finland have also been diagnosed (Varho et al. 2002). Growth retardation becomes obvious, with varying endocrine abnormalities. Coarse facial features resemble storage diseases involving the skeletal system. X-ray of the lumbar spine may demonstrate ovoid-shaped vertebrae on lateral views. MRI in Salla disease showing generalised deficiency of myelin with a thin corpus callosum. Later, atrophy becomes evident that may especially affect the cerebellum. As in other mucolipidoses, the EEG showing low voltage traces. Motor and sensory nerve conduction velocities are reduced. The increased excretion of sialic acid in urine is used for diagnosis. Confirmation requires the demonstration of storage of free sialic acid in fibroblasts. No causal treatment is available for patients with Salla disease.

Infantile sialic acid storage disease (ISSD; MIM #269920), also called infantile sialuria or n-acetylneuraminic acid (NANA)
storage disease is an allelic more severe form of the disorder. Unlike Salla disease, ISSD has no particular ethnic prevalence. It has earlier onset, in utero (with fetal hydrops and ascites) or at birth (with hydrops, severe visceral involvement, hepatosplenomegaly often associated with ascites, coarse facies, dysostosis multiplex, severe psychomotor retardation and seizures), and is fatal in early childhood.

FUCOSIDOSIS

Fucosidosis (MIM #230000) is an autosomal recessive lysosomal storage disease caused by defective alpha-L-fucosidase with accumulation of fucosylated glycoconjugates (e.g. glycoproteins and glycolipids) in tissues and urine. It is caused by homozygous or compound heterozygous mutations in the FUCA1 gene encoding the lysosomal enzyme on chromosome 1p36. Clinical features include coarse facial features, visceromegaly, dysostosis multiplex, progressive psychomotor retardation, ocular abnormalities, hearing loss and, with age, angiokeratoma.

Van Hoof and Hers (1968) found the deficiency of alpha-fucosidase activity in the liver of patients with a Hurler-like disorder described by Durand et al. (1969). Based on age at onset, severity of symptoms and length of survival, two different types were proposed: Type 1, a more severe form characterised by onset at about 6 months of age with rapid progression and death within the first decade of life, and Type 2, characterised by milder signs and slower progression with survival into adulthood and with the development of angiokeratoma corporis diffusum. Intermediate cases have been described and an intermediate third type was discussed. Willems et al. (1991) reviewed the literature on 77 patients with fucosidosis and suggested that the distinction between these types did not reflect true genetic heterogeneity, but rather that there seemed to exist a continuous clinical spectrum. The diagnosis of fucosidosis is made by finding the typical chromatographic profile of urinary oligosaccharides. Results are confirmed by measuring the alpha-L-fucosidase activity in leucocytes. Very low to negligible residual enzyme activity is found in patients of all types. Brain MRI showing diffuse hypomyelination, a thin corpus callosum, T1-hyperintensity and T2-hypointensity of the globus pallidus and cerebellar atrophy. Concerning treatment, bone marrow transplantation has been tried in some patients with fucosidosis (Vellodi et al. 1995; Miano et al. 2001). Although progressive increase in alpha-L-fucosidase levels and concomitant improvement in myelination on MRI was observed, there was no clinical improvement in psychomotor development.

PERIPHERAL NEUROPATHY, CENTRAL HYPOMYELINATION, WAARDENBURG SYNDROME AND HIRSCHSPRUNG DISEASE

The association of peripheral neuropathy, central hypomyelination, Waardenburg syndrome and Hirschsprung disease (PCWH; MIM #609136), also called the neurological variant of Waardenburg-Shah syndrome, is caused by heterozygous mutations in the SOX10 gene, encoding a member of the SOX (SRY-related HMG-box) family of transcription factors involved in the regulation of neural crest and peripheral nervous system development, on chromosome 22q13.1. Waardenburg syndrome type 2E and 4C are allelic disorders.

The first case was reported by Inoue et al. (1999) in an 11-year-old Japanese girl with Waardenburg-Shah syndrome and neurological abnormalities, including a severe hypomyelinating leukodystrophy suggestive of PMD and a peripheral neuropathy consistent with Charcot–Marie–Tooth disease type I. Touraine et al. (2000) reported three unrelated European patients and contributed to the delineation of the clinical picture. Together with the clinical features of Waardenburg syndrome (pigmentary abnormalities of the hair, skin and eyes; congenital sensorineural hearing loss; and ‘dystopia canthorum’) and Hirschsprung disease (congenital absence of intrinsic ganglion cells in the myenteric and submucosal plexuses of the gastrointestinal tract), patients show early neurological signs with severe hypotonia and developmental delay, nystagmus, and later on, progressive development of cerebellar ataxia, spasticity, demyelinating sensorimotor peripheral neuropathy and severe intellectual disability. Reduced production of tears, saliva and sweat develop progressively and growth failure is observed in surviving patients. Electrophysiological studies show reduced nerve conduction velocities and absent auditory brainstem responses. Brain MRI showing diffuse hypomyelination. Other MRI findings may be bilateral temporal bone abnormalities, agenesis of the cochlear nerve, agenesis of the olfactory bulbs and hypoplasia or agenesis of the lacrimal and parotid glands (Elmaleh-Berges et al. 2013).

NUCLEOTIDE EXCISION–DNA REPAIR SYNDROMES

Xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD) are rare DNA repair syndromes with photosensitivity of the skin, hair and skin abnormalities, short stature, microcephaly, intellectual disability and various neurological abnormalities. An overlap between xeroderma pigmentosum and TTD, as well as between xeroderma pigmentosum and Cockayne syndrome, may be observed clinically and has also been demonstrated by complementation analysis of cell fusions. Hereditary mutations in the repair and transcription factor DFI1H1 are associated with all three syndromes. White matter abnormalities are restricted mainly to Cockayne syndrome and TTD.

COCKAYNE SYNDROME

Cockayne syndrome is a rare but clinically characteristic disorder first described in 1936 as ‘dwarfism with retinal atrophy and deafness’. It follows an autosomal recessive inheritance.
Mutations in two major genes have been described: the gene ERCC8 encoding the group 8 excision-repair cross-complementing protein on chromosome 5q11 (CSA; MIM #216400) (Henning et al. 1995); and the gene ERCC6 encoding the group 6 excision-repair cross-complementing protein on chromosome 10q11 (CSB; MIM #133540) (Mallery et al. 1998), accounting for approximately 80% of Cockayne syndrome cases (Licht et al. 2003). From a clinical view, Nance and Berry (1992) reviewed 140 cases and distinguished three clinically different types of the disease: (1) classic Cockayne syndrome (the majority); (2) early-onset severe, rapidly progressive type Cockayne syndrome II, with clinical manifestations from birth and shorter survival; and (3) mild, late-onset, slowly progressive form. Mallery et al. (1998) found no correlation between genotype and phenotype among 16 patients with Cockayne syndrome of varying severities. Besides CSA and CSB, mixed forms associating features of Cockayne syndrome and xeroderma pigmentosum exist: XPF/CS (MIM #278780) caused by mutation in the ERCC5 gene on chromosome 13q33; XPC/CS (MIM #610651), caused by mutation in the ERCC3 gene on chromosome 2q21; and XPF/CS; MIM #278760, caused by mutation in the ERCC4 gene on chromosome 16p13. Rapin et al. (2000) reviewed the clinical and molecular features of Cockayne syndrome, xeroderma pigmentosum and the xeroderma pigmentosum – Cockayne syndrome complex.

Affected children show characteristic cachectic dwarfism, and a progeroid facial appearance with prominent chin and nose and large ears. The enophthalmia (sunken eyes) is due to the lack of subcutaneous orbital fat. Decrease height and weight, microcephaly, hearing loss, pigmentary retinopathy, dental caries and cataracts develop. Patients walk with a characteristic stoop, and develop pyramidal and cerebellar symptoms (Rapin et al. 2000). In contrast to other disorders of DNA repair, cancer has not been reported as a feature of classic Cockayne syndrome.

A peripheral neuropathy with reduced nerve conduction velocity and segmental demyelination in teased sural nerve preparations has been reported (Moosa and Dubowitz 1970). In an analysis of 13 cases, Pasquier et al. (2006) found a wide clinical variability of symptoms including conjunctival telangiectasia and skeletal dysplasia with flat vertebral bodies. Neuropathology described thickened leptomeninges, features of a calcifying vasculopathy, cerebral and cerebellar atrophy, and lack of myelin with a tigroid pattern due to preserved islands of myelin. Calcium deposits may be found in the basal ganglia and dentate nuclei as well as in the white matter and cortex of the brain.

CT and MRI show calcifications of basal ganglia, white matter abnormalities (hypomyelination) and cerebellar atrophy (Adachi et al. 2006). CSF may show high lactate levels. Abnormal excretion of organic acids has also been observed. The diagnosis is based on the hypersensitivity to UV light of cultured cells (Lehmann et al. 1993). Prenatal diagnosis of Cockayne syndrome is possible (Kleijer et al. 2006). No treatment is available, the management is symptomatic.

## TRICHOHIODYSTROPHY WITH PHOTOSENSITIVITY

Trichothiodystrophy with photosensitivity (TTDP; MIM #601675) is an autosomal recessive disorder that may be caused by mutations in at least two genes that encode the two helicase subunits of transcription/repair vector TFIH: ERCC2/XPD gene on chromosome 19q13 (Frederick et al. 1994), accounting for the majority of patients; and ERCC3/XPB gene on chromosome 2q14 (Weeda et al. 1991). Besides these two groups, an exceptional trichothiodystrophy complementation group designated TTDA is caused by mutations in gene GTF2H5 coding for the tenth subunit of TFIH, TFB5, on chromosome 6q25 (Giglia-Mari et al. 2004). Hashimoto and Egly (2009) reviewed the clinical features and genetics of trichothiodystrophies. TTDP is clinically characterised by (sulphur-deficient) brittle and fragile hair, often combined with ichthyosis and nail abnormalities. The abnormalities are usually obvious at birth, with variable clinical expression. Many patients die at a young age, most commonly due to infectious diseases. About half of the patients with TTD exhibit marked photosensitivity, due to abnormalities in excision repair of ultraviolet-damaged DNA. However, as in Cockayne syndrome, cancer is rare. Brain MRI showing a lack of myelination in supratentorial white matter with periventricular predominance and homogeneous involvement of the corpus callosum. The hair showing the characteristic ‘tiger-tail banding’ pattern with polarising microscopy, and contains decreased high-sulphur matrix proteins. The DNA excision repair defect can be demonstrated in fibroblasts.

Non-photosensitive trichothiodystrophy (TTDN; MIM #234050) is a distinct disorder without photosensitivity caused by mutations in the MPLKIP/TTDN1 gene on chromosome 7p14 (Nakabayashi et al. 2005). The encoded protein is thought to be involved in regulating mitosis and not in nucleotide excision repair.

## MULTISYNTHETASE-RELATED HYPOMYELINATION LEUKODYSTROPHIES

### DARS-Related Hypomyelination/ Hypomyelination with Brainstem and Spinal Cord Involvement and Leg Spasticity

Hypomyelination with brainstem and spinal cord involvement and leg spasticity (HBSL; MIM #615281) is a recently described autosomal recessive leukoencephalopathy caused by homozygous or compound heterozygous mutations in the DARS gene on chromosome 2q21.3 (Taft et al. 2013). The gene DARS encoding the cytoplasmic enzyme aspartyl-tRNA synthetase, a member of a multi-enzyme complex amino-acyl-tRNA synthetase (multisynthetase), that functions in mediating the attachment of amino acids to their cognate tRNAs.
Taft et al. (2013) reported ten patients from seven unrelated families from all over the world with severe lower limb spasticity associated with leukoencephalopathy. Most patients presented after normal early psychomotor development, between 4 and 12 months of age, with progressive motor dysfunction, mainly spasticity predominant in the lower limbs, as well as axial hypotonia and loss of motor milestones. None achieved independent walking. Four patients showed mild intellectual disability. Other features included nystagmus and pallor of the optic discs. Brain MRI showed extensive white matter abnormalities involving the supratentorial white matter, brainstem, cerebellar peduncles, and dorsal columns and lateral corticospinal tracts of the spinal cord. The authors noted the phenotypic similarities to the leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL; MIM #611105), which is caused by mutations in the DARS2 gene, coding for the mitochondrial enzyme aspartyl-tRNA synthetase 2 (see the Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation section).

**RARS-Related Hypomyelination**

By performing whole exome sequencing, Wolf et al. (2014) have recently found mutations in the RARS gene in four patients of three families with hypomyelination. The gene RARS, on chromosome 5q35, encodes the cytoplasmic enzyme arginyl-tRNA synthetase for arginine, which is also a component of the multi-enzyme aminoacyl-tRNA synthetase (multisynthetase) complex, like aspartyl-tRNA synthetase, deficiency of which causes HBSL (MIM #615281; see the Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Leg Spasticity section).

Clinically, three of the patients showed a similar picture, presenting around the age of 5–12 months with severe spasticity predominant in the lower limbs, nystagmus, mild ataxia and mild intellectual disability. The fourth patient had a much more severe form with earlier onset and with, in addition, a low level of cognition and lack of visual contact paralleling the early severe atrophy present at brain imaging. None of the patients had clinical evidence of peripheral neuropathy. CSF lactate was normal or only slightly elevated in the more severely affected patient. Brain MRI showed severe lack of myelin in the supratentorial white matter in all four patients. Proton MRS of the white matter showed low choline in all four patients and low N-acetylaspartate and elevated lactate in the more severely affected patient.

With the exception of the more severely affected patient, clinical presentation of patients with RARS-related hypomyelination was very similar to HBSL, especially concerning the severe spasticity. Imaging abnormalities are comparable in both entities regarding supratentorial signal abnormalities. Patients with mutations in the RARS gene, however, did not show the brainstem and spinal cord signal abnormalities typical of HBSL. The authors suggested that it is probable that defects in the multisynthetase complex play an important role in the pathogenesis of hypomyelination.

**GLOBAL CEREBRAL HYPOMYELINATION**

Global cerebral hypomyelination (MIM #612949), also called aspartate-glutamate carrier 1 (AGC1) deficiency, is caused by mutations in the SLCO1A2 gene on chromosome 2q31.1, which encodes the AGC1 protein, also known as aralar, a calcium-binding mitochondrial carrier protein involved in the exchange of aspartate for glutamate across the inner mitochondrial membrane.

Only a few cases have been described to date. Wibom et al. (2009) reported the first case in a girl with delayed development from age 5 months with hypotonia, seizures and episodic apnea from 7 months and, later on, severe psychomotor retardation and spasticity. Plasma lactate was increased. Brain MRI showed a global lack of myelination in the cerebral hemispheres and decreased supratentorial volume. The cerebellum, brainstem, and thalami were essentially normal. There was no apparent lesion in the grey matter. MRS showed decreased NAA. Wolf and van der Knaap (2009) commented, and the authors agreed, that the patient described had a primary defect in the cortical grey matter, rather than a leukoencephalopathy. The reduced peak of NAA found on spectroscopy indicates neuronal degeneration, and impaired formation of myelin can be secondary to neuronal dysfunction.

**DEAFNESS, DYSTONIA AND CEREBRAL HYPOMYELINATION**

Deafness, dystonia, and cerebral hypomyelination (DDCH; MIM #300475) is caused by hemizygous mutations in the BCAP31 gene, encoding a member of the B-cell receptor associated protein 31 superfamily involved in the antero- grade transport of membrane proteins from the endoplasmic reticulum to the Golgi, on chromosome Xq28. DDCH is an X-linked recessive disorder characterised by severe psychomotor development delay, dysmorphic facial features, sensorineural deafness, dystonia, pyramidal signs, increased liver enzymes during febrile illness and hypomyelination on brain imaging with variable cerebral or cerebellar atrophy (Cacciagli et al. 2013).

The gene BCAP31 is a neighbour of the gene ABCD1, responsible for X-linked adrenoleukodystrophy (X-ALD; MIM #300100; see X-linked Adrenoleukodystrophy section). Microdeletions including both genes give rise to the contiguous ABCD1/DXS1375E(BCAP31) deletion syndrome (CADDSS), a disorder with neonatal onset and liver disease, unlike the classic X-ALD due to ABCD1 mutations (Corzo et al. 2002).
A few degenerative disorders involve most parts of both the cerebrum and cerebellum or brainstem structures, without any evidence of storage or specific lesion. They are of proven or likely genetic origin but their mechanism is undetermined. The peripheral nervous system is also affected in the two main conditions of this group, neuro-axonal dystrophy (NAD) and neuronal intranuclear inclusion disease.

NEURO-AXONAL DYSTROPHY (SEITELBERGER DISEASE)

This disease is now included in the group of diseases called neurodegeneration with brain iron accumulation (NBIA) characterised by iron accumulation in the basal ganglia. A number of autosomal recessive NBIA syndromes can present in childhood, most commonly pantothenate kinase-associated neurodegeneration (NBIA1 or PKAN, due to mutations in the PANK2 gene; see Chapter 19) and phospholipase A2 group 6-associated neurodegeneration (NBIA2 or PLAN, associated with genetic defects in PL2G6). PLAN comprises a heterogeneous group of autosomal recessive neurodegenerative disorders associated with genetic defects in the PL2G6 gene (Khaete et al. 2006; Morgan et al. 2006). PL2G6 encodes a calcium-independent phospholipase A2 enzyme, which is involved in phospholipid remodelling and is thought to be integral to maintaining cell membrane homeostasis (Tanaka et al. 2004; Balsinde and Balboa 2005). Alteration or loss of function of this protein may result in the axonal pathology of both the central and peripheral nervous system and brain iron accumulation observed in these conditions. The phenotypic spectrum of PL2G6-related disorders is ever expanding. The classic infantile neuro-axonal dystrophy (INAD; MIM #256600) is a form of PLAN presenting in infancy (infantile PLAN). It accounts for the majority of PLAN cases and the PL2G6 mutation detection rate is particularly high (80–90%) in children with the classic INAD phenotype (Crompton et al. 2010). Allelic disorders are childhood PLAN or atypical NAD including Karak syndrome (MIM #610217) and adult-onset PLAN or early-onset dystonia-parkinsonism (MIM #612953) (Morgan et al. 2006; Kurian et al. 2008; Paisan-Ruiz et al. 2009).

Pathological findings in INAD include the presence of axonal swellings, known as spheroids, formed by branched tubular structures and bundles of filaments with mitochondria in nerve fibres, especially at presynaptic endings. The spheroids are widespread throughout the CNS and are especially numerous in the posterior horns of the spinal cord, Goll and Burdach nuclei, and pallidum, which also contain excess ferric pigment and fat. They are also present in the peripheral nerves, which has been the basis for the diagnosis by peripheral biopsy. Smaller bodies with a similar ultrastructure (eosinophilic bodies) are found in the cortex. There is associated diffuse gliosis of the white matter of the centrum semiovale and degeneration of several long tracts of certain systems (e.g. pyramidal, spinocerebellar) (Aicardi and Castelein 1979). A disturbance of retrograde axonal transport may be the cause of the disease.

Clinical onset is usually between 6 months and 2 years of age, median age 14 months (Aicardi and Castelein 1979; Nardocci et al. 1999b; Gregory et al. 2008; Kurian et al. 2008), often with axial hypotonia or difficulties of ambulation. In some cases, an intercurrent illness can precede symptom presentation, thus mimicking the clinical presentation of a metabolic disorder (Kurian et al. 2008). Progress stops and, after a period of stagnation of weeks to months, frank deterioration appears. Rapidly, there is hypotonia so marked as to suggest the diagnosis of a neuromuscular disease (Aicardi and Castelein 1979). However, pyramidal tract signs appear early even though deep tendon reflexes may be weak or absent. The disease progresses to severe dementia accompanied by increasing spasticity that evolves into decorticate rigidity. Optic atrophy with nystagmus is present in 70% of cases by 3 years of age, and may be reported in the early stages of the disease (Kurian et al. 2008). The majority of children develop spinal deformities such as kyphoscoliosis and limb contractures. Bulbar dysfunction is normally evident in most children by 5 years of age (Kurian et al. 2008). Extrapyramidal features such as dystonia are also reported, more commonly towards the end of the first decade. Epileptic seizures are unusual and frequently a later feature in the disease course (Barontini and Papini 1981) although in certain populations epileptic seizures may be evident at an earlier stage (Wu et al. 2009). Death occurs by 5–10 years, mean age 9 years, and is usually secondary to cardiorespiratory complications, infection, malnutrition and, rarely, status dystonicus (Kurian et al. 2008; Gregory et al. 2008).

The CSF is normal and no specific biochemical marker is known. CT and MRI usually show cerebellar atrophy but no abnormality of density of the white matter. Cerebellar atrophy is a universal feature and often the earliest sign on MRI. Increased T2 signal in the cerebellar cortex and low water diffusion are suggestive (Nardocci et al. 1999a; Sener 2004) and usually increase in severity with age, but not all children have this feature. Cerebellar hypoperfusion has been demonstrated by functional imaging (Kobor et al. 2005). Many children (40–50%) also have evidence of brain iron accumulation (Gregory et al. 2008; Kurian et al. 2008) with increased iron deposition in the globi pallidi (particularly in the medial aspect of the globus pallidus), dentate nuclei, and substantia nigra, which also appears to become increasingly severe with age. High T2 signal and atrophy of the cerebral white matter have also been reported (Kurian et al. 2008). A neurophysiological syndrome, very suggestive of NAD, is virtually constant. It includes: (1) typical electromyography
(EMG) signs of denervation, especially in distal muscles, with normal sensory and motor conduction velocities; (2) high-
amplitude, fast (18–24Hz) activity in waking and sleep EEG
after 18–30 months of age; (3) absent or abnormal visual and
somaesthetic evoked potentials after at least a few months
course. Pathological confirmation of the diagnosis can be
obtained from peripheral biopsies, especially of the skin or
conjunctiva (Fig. 10.11) but also rectal mucosa, sural nerve
and muscle. Brain biopsy is long since unjustified. The pres-
ence of axonal swelling and spheroid body formation is not
specific, as they can also be found in other forms of NBIA.
In recent years, the availability of molecular genetic testing
has eliminated the need for invasive biopsy in the majority
of cases.

Childhood-onset PLAN or atypical NAD is much rarer
than INAD and includes the condition previously described
as Karak syndrome (Mubaidin et al. 2003). It has a later
clinical onset, from 18 months to 6.5 years, mean age
4 years and 3 months, usually with subtle gait abnormalities,
dyspraxia, and speech regression, and the progression is slower
(Morgan et al. 2006; Gregory et al. 2008; Gregory et al.
2009). Over time, many signs of INAD such as optic atrophy,
nystagmus, tetraparesis and seizures appear; however, signs of
adolescent or adult NBIA phenotypes such as extrapyrami-
dal features and neuropsychiatric disturbances become major
features later in the disease course. The lifespan of atypical
NAD is not currently determined. Brain iron accumulation is
a consistent universal feature, involving both globus pallidus
and substantia nigra. Cerebellar atrophy may also be present.
Fast rhythms of EEG have not been reported. Visually evoked
potentials may be delayed with reduced amplitude. EMG,
nerve conduction studies, and electroretinogram are reported
to be normal. Histopathological findings are identical to those
described for INAD.

In a significant proportion of children with NBIA there is
currently no known genetic diagnosis (Gregory et al. 2009).
This group display marked clinical heterogeneity, with age at
presentation that varies greatly from symptom onset in infancy
(often with rapid disease progression) to initial presentation in
the third to fifth decade (often associated with slower disease
progression), and diverse clinical signs including pyramidal,
extrapyramidal, and ophthalmological features. Evidence of
iron accumulation in the globus pallidus and substantia nigra is
seen on brain MRI.

The differential diagnosis of INAD includes a large num-
ber of disorders, among which infantile metachromatic leu-
kodystrophy may have a very similar presentation; also the
pantothenate kinase 2 (PANK2)-associated neurodegenera-
tion (formerly Hallervorden–Spatz disease) (see Chapter 19),
accounting for approximately 50% of childhood NBIA dis-
orders. It is clinically different as it presents mostly with
extrapyramidal features, and is also genetically distinct by
molecular study.

Only supportive treatment is available for any form of
NAD. Genetic counselling and prenatal diagnosis is now
possible in cases with identification of the causative gene.

**DISORDERS INVOLVING PREDOMINANTLY THE GREY MATTER**

These include the neuronal ceroid lipofuscinoses, which also
feature more diffuse involvement of the CNS, and a group
of poorly defined conditions known as the poliodystrophies.

**POLIODYSTROPHIES**

Poliodystrophies form a heterogeneous group of disor-
ders known collectively as Alpers or Alpers-like disease. The
poliodystrophies are characterised pathologically by predom-
inant involvement of the grey matter, which is reduced in
volume and of abnormally firm consistency. At a late stage,
the brain is usually grossly atrophic, the so-called 'walnut
brain'. Neurons are greatly reduced or lacking altogether, or
in a focal or laminar topography. There is marked glial pro-
liferation, often associated with a spongy appearance of the
neuropil, hence the term glioneuronal spongy degeneration
used by some authors. At an early stage, the focal distribu-
tion of lesions is remarkable or they may be minimal. Such
grey matter degeneration is difficult to differentiate from
other conditions such as hypoxic sequelae, hypoglycaemia or
postepileptic encephalopathy, and undoubtedly some such
cases have been included among reports of poliodystrophy.
Therefore, the diagnosis should be based not only on patho-
logical findings but also on the notion of a progressive ill-
ness. Most authentic cases of poliodystrophy have an estab-
lished or probable genetic origin with an autosomal recessive
inheritance.
The best-defined group among the poliodystrophies is the progressive neuronal degeneration of childhood (PNDC) with hepatic involvement or Alpers–Huttenlocher syndrome, an autosomal recessive progressive disorder considered today as an infantile or childhood-onset polymerase-γ-related disorder (Saneto and Cohen 2013) and also known as mitochondrial DNA depletion syndrome 4A (Alpers type; MIM #203700), caused by homozygous or compound heterozygous mutations in the nuclear gene POLG on chromosome 15q26.1 encoding mitochondrial DNA polymerase-γ. Although the first report of this condition dates from 1890 (Bullard 1890), Alpers described the clinical picture in 1931 (Alpers 1931). The description of the associated hepatic features and CSF findings and the confirmation of autosomal recessive inheritance happened 45 years later (Huttenlocher et al. 1976). More than 20 years later, Harding described 32 patients with a distinctive liver and brain pathology, defining the typical clinical course of the disease (Harding 1990). The biochemical and enzymatic relevance of polymerase-γ to Alpers–Huttenlocher syndrome was established by Navaux et al. with their description of mitochondrial DNA depletion and reduced POLG enzyme activity in a child with Alpers syndrome (Navaux et al. 1999). In 2004, mutations in POLG were shown to be responsible for the clinical entity of Alpers–Huttenlocher syndrome (Navaux and Nguyen 2004).

The onset of this disorder is usually between 2 and 4 years of age (range 3 months to 8 years) (Harding 1990; Horvath et al. 2006; De Vries et al. 2007), but some late cases are possible, with a second peak onset between 17 and 24 years (Harding 1995; Wiltshire et al. 2008). Seizures and developmental regression appear insidiously, often in a child whose initial development had been somewhat slow. Seizure semiology can vary from patient to patient, and changes as the disease progresses in many patients. Focal, asymmetric, occipital-predominant seizures occur at onset (Wolf et al. 2009; Saneto et al. 2010a). As the disease progresses, most patients manifest repeated episodes of status epilepticus and epilepsy partialis continua (Navaux et al. 1999; Gauthier-Villars et al. 2001; Navaux and Nguyen 2004; Hakonen et al. 2005; Winterhun et al. 2005; Horvath et al. 2006; Tzoulis et al. 2006; Saneto et al. 2010a). Myoclonus and myoclonic seizures become more prominent and almost continuous, and both are refractory to medical treatment. Bilateral spasticity, opisthotonus and decerebration eventually set in, often after several episodes of partial status epilepticus. Blindness is common and may be due either to occipital cortical involvement, which is often prominent, or to optic atrophy. The EEG is always severely abnormal with multifocal paroxysmal activity. Boyd et al. (1986) emphasised the occurrence of large slow waves with superimposed small-amplitude polyspikes often asymmetrically located over the occipital regions. Visual evoked potentials are grossly abnormal, with a normal electroretinograph (ERG). CSF protein may be increased. Neuroimaging indicates progressive brain atrophy without signal change. PNDC runs a fatal course. After seizures appear, the disease becomes rapidly progressive. Death usually occurs within 4 years of onset (Harding 1995; Wiltshire et al. 2008). In other cases, disease progression is slower (Tzoulis et al. 2006; Saneto and Navaux 2010b). Signs of hepatic disease that may end in terminal liver failure often become obvious only late in the course or in autopsy findings (Harding 1995). Some cases occur without hepatic failure (Isohanni et al. 2011). Exposure to valproic acid inducing severe liver dysfunction has been a defining feature of Alpers–Huttenlocher syndrome (Bicknese et al. 1992; Navaux and Nguyen 2004; Nguyen et al. 2005; Wolf et al. 2009; Saneto et al. 2010a). Such cases may be easily mistaken for valproate hepatotoxicity (Bicknese et al. 1992; Delarue et al. 2000). The histochemical changes induced by valproic acid are identical to those observed without exposure (Harding 1990; Nguyen et al. 2006) and differ from those in other chemically induced or toxic liver disorders (Simonati et al. 2003). The exact mechanism of liver alterations remains elusive.

Mutations in POLG are associated with other mitochondrial disorders involving the gastrointestinal system, muscle and/or CNS. More than 180 pathogenic mutations of POLG, with both dominant and recessive modes of inheritance, have been described resulting in a wide phenotypic spectrum. Recessive mutations represent the predominant disease inheritance pattern and they can occur throughout all exons in POLG and produce several clinical syndromes as well as multiple organ system diseases with onset throughout the lifespan that do not cluster within distinct phenotypic syndromes (Wong et al. 2008; Saneto and Navaux 2010b; Tang et al. 2011). Furthermore, other mitochondrial DNA depletion syndromes due to mutations in other genes exist, resulting in hereditary progressive disorders with variable age at onset and involvement of multiple organs, including in some cases the liver and the brain (Finsterer and Ahting 2013; El-Hattab and Scaglia 2013; Uusimaa et al. 2014).

**THE CEROID LIPOFUSCINOSES**

**Neuronal Cerebral Lipofuscinosis (Batten Disease)**

The neuronal ceroid lipofuscinoses (CLNs) are a clinically and genetically heterogeneous group of disorders, collectively called Batten disease, characterised by the intracellular storage of certain lipopigments that present morphological and tinctorial similarities with lipofuscin, an autofluorescent ‘wear-and-tear’ pigment accumulating in the cells of many animal tissues during ageing. They constitute a special group within the inherited lysosomal storage disorders. Zeman and Dyken (1969) referred to these conditions as the ‘neuronal ceroid lipofuscinoses’. Goebel (1995) provided a comprehensive review of the CLNs and noted that they are possibly the most common group of neurodegenerative diseases in children.

CLNs are a panethnic group of diseases; however, local variations are marked. Their incidence rates vary from 1 : 67 000 in...
Italy and Germany to 1:14,000 in Iceland, and their prevalence rates vary from 1:1,000,000 in some regions to 1:100,000 in the Scandinavian countries (Williams 2011). Some forms seem to have a higher frequency in certain populations, as is the case of CLN6 in Southern European countries (Teixeira et al. 2003) and CLN7 in certain Mediterranean populations (Aiello et al. 2009; Aldahmesh et al. 2009; Kousi et al. 2009; Stogmann et al. 2009).

Despite the clinical and genetical heterogeneity, all forms of NCL share a remarkably uniform morphological phenotype, the basis of the NCL concept (Haltia 2003; Haltia et al. 2011). All forms of NCL share at least two essential features: (1) Autofluorescent, electron-dense, periodic acid-Schiff (PAS) and Sudan black B-positive granules, resistant to lipid solvents, accumulate in the cytoplasm of most nerve cells and, to a lesser extent, in many other cell types. (2) This storage is associated with progressive and selective loss of neurons, particularly in the cerebral and cerebellar cortex and, less constantly, in the retina, leading to cognitive, motor and visual deterioration with refractory epilepsy.

Although the term lipofuscin, which designates the pigment that accumulates in neurons with age, is often used, the lipopigments that constitute the storage substance, termed ceroid, differ (Seehafer and Pearce 2006). The chemical nature of these pigments is not fully characterised. A major component of the pigment stored in infantile and juvenile ceroid lipofuscinosis comprises subunit C of the respiratory chain enzyme ATP-synthase. Ceroid accumulates mainly in lysosome-like structures that give a positive acid phosphatase reaction. Their ultrastructural appearance is also distinct. The lipopigment pattern seen most often in all forms of CLN1, in CLN10, as well as in the autosomal dominant adult-onset form CLN4b is referred to as granular osmiophilic deposits (GRODs). The pattern most often observed in CLN2 is curvilinear, and in CLN3 fingerprint, less frequently mixed. The other forms of CLN often show combinations of curvilinear, rectilinear and fingerprint profiles (for review see Anderson et al. 2013).

Since 1995, over 360 mutations in 13 different genes underlying the various established human forms of NCL have been identified (Kousi et al. 2012). The NCL genes are of vital importance for the maintenance of cerebral neurons. Intracellular localisation and function (where known) of the defective proteins are different: four NCL types are caused by defects in lysosomal enzymes (CLN1, CLN2, CLN10, CLN13), others by defects in transmembrane proteins (CLN3, CLN6, CLN7, CLN8) (Jalanko and Braulke 2009). Mutations in an ATPase gene (CLN12) (Bras et al. 2012) and a potassium channel gene (CLN14) (Staropoli et al. 2012) also cause NCL disease. The recently identified CLN4 gene (DNA1/CS) codes for a protein with putative function in synapses (Arsov et al. 2011). How these genetic defects lead to neurodegeneration is still not well understood.

The original classification of the NCLs (Zeman 1976) was based on their clinical and neuropathological phenotypes, mainly on the age at onset of the clinical manifestations and the ultrastructure of the storage cytosomes. The advances in molecular genetics have made this old classification problematic, since different mutations in a given gene may give rise to varying phenotypes, including widely different ages at onset. A purely genetic classification of the NCLs has therefore been proposed, in which they are classified numerically according to the underlying gene defect into 14 genetic forms from CLN1 to CLN14, regardless of the age at onset (Mole et al. 2005). A new NCL classification that identifies each CNL both genetically and clinically has been developed in an attempt to be universally understood and of value for clinicians responsible for diagnosis and treatment, research scientists, patients and families (Mole et al. 2011; Williams et al. 2011; Williams and Mole 2012). It classifies the NCLs using both the defective gene as well as the age at onset (Table 10.6). In 13 of the 14 NCL forms described to date, the responsible genes are currently isolated and characterised, located on different chromosomes. All but one (the autosomal dominant adult-onset CLN4b) show an autosomal recessive mode of inheritance, and the age at onset can vary, resulting in congenital, infantile, late infantile, juvenile and adult forms. The clinical manifestations are the result of the progressive degeneration of CNS and, less constantly, of retinae. In the childhood forms, the clinical picture is dominated by epilepsy, myoclonus and cognitive deterioration, expressing the predominant involvement of the grey matter (Santavuori et al. 2001), as well as by progressive loss of vision, while the adult forms usually present with dementia.

The diagnosis of NCL may be difficult especially in the less usual forms. Neurophysiological features, such as an abnormal ERG and a peculiar response of the EEG to slow light stimulation (1–3Hz), are of value in late infantile and some adult-onset forms. Brain atrophy on neuroimaging is usually present early in the childhood onset forms, but it may also not be found in the first year and it may be absent in the adult-onset forms. A decreased T2 signal in the thalami found in CLNs 1, 2, 3, 5, 6 and 7 is suggestive but not specific (Autili et al. 2007). Cerebellar atrophy and leukoencephalopathy are also frequently found (Jadav et al. 2012).

The term neuronal ceroid lipofuscinosis is not entirely accurate as the lipopigment is also found in many extraneural tissues. Most diagnostic brain biopsy investigations were carried out before this widespread accumulation of lipopigments in extracerebral tissues had been recognised, and have then been superseded by those of skin, rectum, skeletal muscle and even blood lymphocytes, that have traditionally been the basis of the diagnosis. The demonstration of low activity of the lysosomal enzyme in some forms, or the identification of the responsible gene mutations in most, now allows accurate diagnosis. However, ultrastructural examination of extracerebral tissues is still necessary in atypical cases, particularly the late infantile onset variants and the relatively stable figures (10–12%) of molecularly undetermined cases.

Prenatal diagnosis has been made by demonstration of the enzyme activity deficiency or the presence of the typical ultrastructural storages in chorionic villus biopsies in CLNs 1, 2 and 3, less frequently in other forms. This procedure has been
<table>
<thead>
<tr>
<th>Disease</th>
<th>Alternative titles/names</th>
<th>Clinical phenotypes</th>
<th>Phenotype MIM no.</th>
<th>Gene</th>
<th>Gene MIM no.</th>
<th>Chromosome</th>
<th>Gene product</th>
<th>Type of inheritance</th>
<th>Storage cytosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceroid lipofuscinosis, neuronal, 1</td>
<td>Infantile classic, Santavuori disease, Santavuori-Haltia disease</td>
<td>Infantile classic, late infantile, juvenile, adult</td>
<td>256730</td>
<td>PPT1/CLN1</td>
<td>600722</td>
<td>1p34.2</td>
<td>PPT1</td>
<td>Autosomal recessive</td>
<td>GRODs</td>
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<td>TPP1/CLN2</td>
<td>607998</td>
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<td>TPP1</td>
<td>Autosomal recessive</td>
<td>Curvilinear</td>
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<td>204200</td>
<td>CLN3</td>
<td>607042</td>
<td>16p11.2</td>
<td>CLN3</td>
<td>Autosomal recessive</td>
<td>Fingerprint Less frequently mixed (fingerprint and rectilinear and less frequently curvilinear)</td>
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<td>Adult</td>
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<td>CLN6</td>
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<td>15q23</td>
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<td>Autosomal recessive</td>
<td>Fingerprint</td>
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<td>Adult autosomal dominant</td>
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<td>DNAJC5/CLN4</td>
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<td>20q13.33</td>
<td>DNAJC5</td>
<td>Autosomal dominant</td>
<td>GRODs</td>
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<td>Finnish variant late infantile, variable age at onset</td>
<td>Late infantile, juvenile, adult</td>
<td>256731</td>
<td>CLN5</td>
<td>608102</td>
<td>13q22.3</td>
<td>CLN5</td>
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<td>Mixed (curvilinear and fingerprint, and less frequently granular and rectilinear)</td>
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<td>Lake-Cavanagh Early juvenile/Indian variant Late infantile</td>
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<td>CLN6</td>
<td>606725</td>
<td>15q23</td>
<td>CLN6</td>
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</tr>
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<td>Turkish variant Late infantile</td>
<td>Late infantile, juvenile, adult</td>
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<td>MFSD8/CLN7</td>
<td>611124</td>
<td>4q28.2</td>
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<td>607837</td>
<td>8p23.3</td>
<td>CLN8</td>
<td>Autosomal recessive</td>
<td>Mixed (curvilinear and fingerprint, and less frequently granular and rectilinear)</td>
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<tr>
<td>Disease</td>
<td>Alternative titles/names</td>
<td>Clinical phenotypes</td>
<td>Phenotype MIM no.</td>
<td>Gene</td>
<td>Gene MIM no.</td>
<td>Chromosome</td>
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<td>Type of inheritance</td>
<td>Storage cytosomes</td>
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<tr>
<td>Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant</td>
<td>Northern epilepsy/progressive epilepsy with mental retardation intellectual disability</td>
<td>Progressive epilepsy with mental retardation intellectual disability</td>
<td>610003</td>
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<td>607837</td>
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<td>Autosomal recessive</td>
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<td>Juvenile</td>
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<td></td>
<td></td>
<td></td>
<td>Yet to be better defined (fingerprint in blood lymphocytes)</td>
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<td>Congenital classic, late infantile, juvenile, adult</td>
<td>610127</td>
<td>CTSD/CLN10</td>
<td>116840</td>
<td>11p15.5</td>
<td>Cathepsin D</td>
<td>Autosomal recessive</td>
<td>GRODs (absent in extracerebral tissues in late onset forms)</td>
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<tr>
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<td>Adult</td>
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<td>138945</td>
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<td>Progranulin</td>
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<td>Yet to be better defined (fingerprint in skin biopsy)</td>
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<td>Juvenile</td>
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<td>ATP13A2/CLN12</td>
<td>610513</td>
<td>1p36.13</td>
<td>P type ATPase</td>
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<td>Ceroid lipofuscinosis, neuronal, 14</td>
<td>Progressive myoclonic epilepsy 3, with or without intracellular inclusions</td>
<td>Infantile, epilepsy, progressive myoclonic epilepsy 3</td>
<td>611726</td>
<td>KCTD7/CLN14</td>
<td>611725</td>
<td>7q11.21</td>
<td>Potassium channel tetramerisation domain-containing protein 7</td>
<td>Autosomal recessive</td>
<td>Yet to be better defined (fingerprint and GRODs in blood lymphocytes, rectilinear in nerve)</td>
</tr>
</tbody>
</table>

GRODs, granular osmophilic deposits.
replaced by molecular testing in at-risk pregnancies and for suspected carriers.

In 1998 an electronic CLN Mutation Database was created, maintained by Dr Sara Mole at University College London. The database is now part of the ‘NCL Resource – a gateway for Batten disease’ (www.ucl.ac.uk/ncl/index.shtml), providing up-to-date information on the NCLs for clinicians, families and researchers on a free access basis.

To date, there is no curative treatment for any of the NCLs. Anticonvulsant treatment is essential in most types. Sodium valproate and/or clonazepam are often effective, but antiepileptic treatment should be individualised and seizures may be totally refractory. Supportive care to the patients and families is essential and helps lessen the impact of these devastating diseases. In recent times, preclinical experiments in the murine model of infantile NCL have shown that gene therapy, enzyme replacement, stem cell transplantation and small-molecule drugs, alone and especially in combination, can significantly slow disease progression (for review see Kohan et al. 2011; Sands 2013). Some of them have already been tried in children with NCL (Selden et al. 2013). Similar approaches may be useful to treat other forms of NCL, but different targets will need to be identified in order to design novel therapeutic strategies.

**CLN1**

**Infantile Classic; Santavuori Disease; Santavuori-Haltia Disease**

CLN1 is the classic form of infantile-onset CLN, also known as Santavuori disease or Santavuori-Haltia disease. It is due to homozygous or compound heterozygous mutations in the gene *PPT1/CLN1* on chromosome 1 (1p34.2) that codes for the enzyme palmitoyl protein thioesterase (PPT1), a lysosomal enzyme involved in the catabolism of lipid-modified proteins during lysosomal degradation (Camp et al. 1994). The early development of affected infants is normal. From 6 to 12 months of age, intellectual deterioration and ataxia are the main features. Anxiety and autistic-like features may be prominent, together with the abnormal stereotypic hand movements (‘knitting movements’) that may wrongly suggest the diagnosis of Rett syndrome (see Chapter 5). Myoclonic jerks appear during the second year of life and there is progressive microcephaly due to brain atrophy. Optic atrophy and macular and retinal degeneration without pigment aggregation are frequent, and the ERG is always extinguished, except perhaps in the first few months of the illness. The EEG showing progressive slowing and loss of amplitude leading to an isoelectric tracing (‘vanishing EEG’) during the third year of life (Santavuori 1988). Seizures may not be as prominent as in later onset forms. From 3 to 4 years of age, the disease appears to be ‘burnt out’, spasticity develops and the children remain vegetative without contact with their surroundings until death between 6 and 15 years (Santavuori et al. 1993).

The disease produces an extraordinary degree of brain atrophy. This is well demonstrated by MRI that showing, in addition hypodensity of the thalami, a peripheral ring of increased T2 signal around the ventricles and a reversal of the normal white–grey contrast in late stages (Vanhanen et al. 1995). Surviving neurons, as well as a number of extraneural cells, contain large amounts of ceroid with a homogeneous, finely granular internal structure (Fig. 10.12). Extracerebral storage cytosomes are commonly seen in muscle, eccrine sweat glands of the skin, ganglion cells of the enteric nervous system and to a lesser extent circulating activated macrophages and fibroblasts. Skin biopsy or blood sample for lymphocyte examination and less frequently rectal biopsy are used for the assessment. The storage cytosomes are membrane-bound granular osmiophilic deposits (GRODs). No vacuolated lymphocytes are found. The demonstration of low activity of the enzyme PPT1 or the analysis of the mutation confirms the diagnosis.

Beside the classic infantile-onset CLN1, distinct mutations of the *CLN1* gene can express later in life, giving rise to a late infantile-onset form, a juvenile-onset form and an adult-onset form of CLN1. Diagnosis, as in the infantile-onset form of CLN1, is through testing of PPT1 activity and mutation analysis.

Late infantile-onset CLN due to *CLN1* mutations presents between the age of 1 and 4 years with visual and cognitive decline followed by ataxia and myoclonus (Bonsignore et al. 2006).

Juvenile-onset CLN due to *CLN1* mutations (Kalviainen et al. 2007) presents between the ages of 5 and 10 years with cognitive decline most commonly as the earliest symptom. Seizures may be prominent and diverse in type. Motor decline occurs, but there is typically neither parkinsonism nor myoclonus. Spasticity and ataxia may develop. Vision loss is late in this form, occurring usually between the ages of 10 and 14 years.

Adult-onset NCL due to *CLN1* mutations (Ramadan et al. 2007) presents after 18 years of age with cognitive decline and depression, followed by ataxia, parkinsonism and vision loss.

**Figure 10.12 Late infantile neuronal ceroid lipofuscinosis.** Skin biopsy: inclusion containing curvilinear profiles. (Courtesy Dr M-L Arsenio Nunes, Hôpital de la Salpêtrière, Paris.)
CLN2

Late Infantile Classic; Janský–Bielschowsky Disease

CLN2 is the classic form of late infantile onset CLN, also known as Janský–Bielschowsky disease. It is due to homozygous or compound heterozygous mutations in the gene TPP1/CLN2 on chromosome 11 (11p15.4), which codes for the lysosomal enzyme tripeptidyl peptidase 1 (TPP1). The clinical onset is between 18 months and 4 years of age (Steinfeld et al. 2002). The first symptom is an arrest and rapid regression of development, usually in the second or third year of life. Epilepsy is the prominent feature but usually begins after 30 months of age, soon followed by language regression, dementia and marked ataxia. Seizures may be diverse in type and are often refractory to treatment. They are often myoclonic and are associated with erratic and intention myoclonus, and may simulate Lennox-Gastaut syndrome or other myoclonic epilepsies. Loss of motor skills and spasticity develop rapidly and the children become bedridden by 3.5–6 years of age. Visual failure is usually late: after the age of 6 years. Retinal degeneration, more visible in the macula, and optic atrophy usually appear by 3–4 years of age, and at onset even the ERG may be normal. Death occurs between 6 and 15 years of age.

The neurophysiological picture is characteristic. The EEG showing, in addition to multifocal spikes and slow background rhythm, a peculiar response to photic stimulation at a low rate, each flash producing a spike in the posterior scalp regions (Harden and Pampiglione 1982). The ERG is extinguished. Visual evoked potentials and somatosensory evoked responses are also very large, although VEPs may become abolished at a late stage (Fig. 10.13).

Neuroimaging demonstrates brain atrophy less marked than in infantile-onset CLN1. Extracerebral tissues show cytosomes containing curvilinear profiles (see Fig. 10.12). The lymphocytes are not vacuolated. The demonstration of low activity of the enzyme TPP1 or the analysis of the mutation allows the diagnosis.

CLN3

Juvenile Classic, Batten Disease; Vogt-Spielmeyer Disease; Spielmeyer-Sjögren Disease

CLN3 is the classic form of juvenile-onset CLN, also known as Batten disease, Vogt-Spielmeyer disease or Spielmeyer-Sjögren disease. It is due to homozygous or compound heterozygous mutations in the gene CLN3 on chromosome 16 (16p11.2) that codes for CLN3, a membrane protein of 438 amino acids involved in lysosomal function. It presents between the ages of 4 and 7 years with insidious onset of visual loss caused by retinal degeneration, which begins with hemeralopia and leads to very low acuity in about 2 years. Seizures appear in most cases after 2 or 3 years, and they are well-controlled with medication, at least initially. Myoclonic seizures are common but other generalised, and partial seizures may also supervene. Deterioration is initially absent or mild but behavioural disturbances such as angry outbursts, physical violence, and anxiety with features of depression may be prominent, often leading to a misdiagnosis of a psychiatric condition. A special type of dysarthria with precipitate and indistinct emissions becomes obvious by 10–15 years of age. Neurological signs develop slowly and include extrapyramidal manifestations (parkinsonism with tremor and rigidity; sometimes responsive to L-DOPA) and slight cerebellar and pyramidal signs. In addition to the neurological features, CLN3 patients manifest a cardiac conduction abnormality in the second decade of life. The course is relentlessly progressive leading to death between 15 and 30 years of age.

Ophthalmological examination reveals macular degeneration with pigment aggregates, present from 10 years onward. The EEG may show pseudoperiodic bursts of high-amplitude slow waves or a low-amplitude, rather featureless tracing (Harden and Pampiglione 1982). The ERG and VEPs are decreased or abolished early in the course. Neuroimaging showing mild to moderate atrophy. Extensive calcification is present pathologically and may be apparent on CT.

Lymphocytes are usually vacuolated and show storage with a predominance of fingerprint profiles. The ultrastructural examination of other extracerebral tissue also showing storage with a predominance of fingerprint profiles (Fig. 10.13), but mixed populations of cytosomes with fingerprint, rectilinear and, less frequently, curvilinear profiles may be found. Diagnosis relies on the demonstration of these morphological features and on mutations in CLN3, where a typical deletion is found in the wide majority of cases.
**Chapter 10 Heredodegenerative Disorders**

**CLN4**

**Classic Adult-Onset CLN; Kufs Disease**

Classic adult-onset CLN, also known as Kufs disease, is a CLN without retinal involvement. Berkovic et al. (1988) separate two phenotypes: one characterised by progressive myoclonic epilepsy and neuropsychiatric changes, also observed by Sadzot et al. (2000), and another one, characterised by dementia and motor, cerebellar and extrapyramidal manifestations. These two classic phenotypes correspond to two currently well differentiated CLNs: (1) CLN4 type A, autosomal recessive, which is actually due to mutations of CLN6, other mutations of which are also responsible for CLN6 (Arsov et al. 2011), and (2) CLN4 type B, autosomal dominant, due to mutations of DNAJC5/CLN4 (Noskova et al. 2011; Cadieux-Dion et al. 2013). Both types have their onset around age 30 years, and neither develops retinal degeneration or blindness.

CLN4 type A, also known as autosomal recessive adult-onset CLN4 or Kufs type A variant of adult-onset CLN is caused by homozygous or compound heterozygous mutations in the CLN6 gene on chromosome 15q21-q23, the same responsible for the CLN6, therefore this form can also be classified as adult-onset CLN6. It has an onset around 30 years of age with progressive myoclonic epilepsy followed by development of dementia and ataxia. Dysarthria is prominent. There is no vision loss. Death typically occurs within 10 years. The EEG may show a remarkable response to photic stimulation, with high-amplitude spikes synchronous with flashes at low rhythm of repetition. Vacuolated cells can be found in skin and rectal biopsies and ultrastructural investigations may reveal aggregates of fingerprint profiles surrounded by a single membrane of lysosomal origin. Ultrastructural investigation of blood lymphocytes is not helpful. Mutations in the CLN6 gene are diagnostic. Arsov et al. (2011) noted the striking phenotypic differences between patients with earlier-onset CLN6 and patients with CLN4a or adult-onset CLN6. Patients with earlier-onset CLN6 have retinal involvement, whereas none of the Kufs syndrome patients had retinal involvement. The authors suggested that CLN4 type A or adult-onset CLN6 patients may have some residual mutant protein function or that there are other disease modifiers.

CLN4 type B, also known as autosomal dominant adult-onset CLN4, autosomal dominant Kufs disease or Parry type variant of adult-onset CLN is caused by heterozygous mutations in the gene DNAJC5/CLN4 on chromosome 20q13.33 (Noskova et al. 2011; Cadieux-Dion et al. 2013), that codes for DNAJC5, a cysteine-string protein alpha acting in synaptic vesicles (Noskova et al. 2011). This is the only known autosomal dominant NCL. Onset occurs after age 30 years, and the clinical picture, dominated by dementia and progressive motor cerebellar and extrapyramidal manifestations, includes ataxia, dementia, seizures and myoclonus with no visual loss. Granular osmiophilic deposits (GRODs) are the cytosomes observed in brain tissue and, to a lesser extent, in extracerebral biopsies, including blood lymphocytes. Diagnosis depends on finding mutations in DNAJC5/CLN4.

**CLN5**

**Finnish Variant Late Infantile; CLN with Variable Age at Onset**

CLN5, also known as Finnish variant late-infantile-onset CLN (Wisniewski et al. 1993) or CLN with variable age at onset, is caused by homozygous or compound heterozygous mutations in the gene CLN5 on chromosome 13q22.3, that codes for a soluble lysosomal protein with unknown function (Isosomppi et al. 2002). Despite the name, it occurs worldwide (Savukosky et al. 1998; Moore et al. 2008; Lebrun et al. 2009; Xin et al. 2011). Age at onset in the late infantile onset form is more variable (4–7 years) than in classic late infantile onset CLN (CLN2), and apart from the late infantile onset, some juvenile and even adult-onset CLN5 cases have been described (Pineda-Trujillo et al. 2005; Xin et al. 2011). In the late infantile onset forms, mean age at onset is 5.6 years, and clinical onset commences usually with cognitive deterioration or ataxia. Visual symptoms (macular dystrophy and progressive optic atrophy), epileptic manifestations and neurophysiological abnormalities are observed after 7–8 years of age, and the course is slower than in the classic late infantile onset. The lipopigment patterns observed most often in CLN5 comprise mixed combinations of curvilinear and fingerprint and, less frequently, rectilinear and granular profiles. Diagnosis depends on analysis of the CLN5 gene.

**CLN6**

**Lake-Cavanagh, Early Juvenile; Indian Variant, Late Infantile-Onset**

Mutations affecting the CLN6 gene are related to a wide phenotypic spectrum. Thus, CLN6 gene mutations can give rise to Lake-Cavanagh early juvenile CLN (Lake and Cavanagh 1978), to Indian variant late infantile-onset CLN (Sharp et al. 1997), as well as to adult-onset form (adult-onset CLN6, CLN4a or Kufs type A variant of adult-onset CLN, see above). The CLN6 gene on chromosome 15q21-q23 encodes a conserved, transmembrane polytopic protein of the endoplasmic reticulum (CLN6) whose function has yet to be identified (Sharp et al. 2003). The relevance of the autophagolysosomal compartment observed in human fibroblasts, however, suggests that the mutated protein CLN6 may hamper lysosomal function. Mutations in the CLN6 gene have worldwide distribution, with elevated frequency in Southern European countries compared to those further North (Teixeira et al. 2003).

The clinical features of CLN6 disease of childhood onset are similar to those of classic late infantile CLN (CLN2), and to variants associated with mutations in the CLN7 or CLN8. The age at onset may vary from 18 months to 8 years. The rate of disease progression may vary, with a relatively slower course, but the disease symptoms are similar to the other late infantile CLN, with motor delay, dysarthria, ataxia, vision loss and
seizures. Seizures are an early feature, starting before age 5 years in the majority of patients. Vision loss occurs also early in about half of patients. Deterioration is rapid leading to severe disability in adolescence. Death usually occurs by the end of the second decade in life. Both ERG (extinction) and evoked potentials (giant cortical evoked potentials) are abnormal. Ultrastructural analysis of skin biopsy or blood lymphocytes is useful, particularly during the early stages of the disease. The storage population in CLN6 disease is mixed and pleomorphic: curvilinear and fingerprint profiles are the major components, and rectilinear and granular material less frequently seen. Diagnosis depends on analysis of the CLN6 gene.

CLN7

Turkish Variant; Late Infantile

CLN7 has been described in Turkish patients (Ranta et al. 2004; Topçu et al. 2004). The clinical picture was similar to that of the Finnish variant (CLN5) but with a greater severity. It is caused by homozygous or compound heterozygous mutations in the gene MFSD8/CLN7 on chromosome 4q28.3, that codes for the protein MFSD8, a putative lysosomal transporter (Siintola et al. 2007). Despite the name, it occurs worldwide, but its frequency seems to be higher among Mediterranean populations (Aiello et al. 2009; Aldahmesh et al. 2009; Kousi et al. 2009; Stogmann et al. 2009). Age at onset is 2−7 years, mean 5.1 years. The initial symptom is typically seizures followed by myoclonus, progressive motor impairment with ataxia, speech and cognitive deterioration, vision loss, and behavioural and sleep disturbances. The rate of progression is quite steady, most patients becoming non-ambulatory within 2 years after onset and death occurs within the second decade. Cases with later onset and protracted course have been described (Kousi et al. 2009). Both ERG (extinction) and evoked potentials (giant cortical evoked potentials) are abnormal. The features distinguishing the CLN7 from other late infantile onset CLNs include the more severe clinical course and the presence of fingerprint profiles alone or mixed with curvilinear, rectilinear and less frequently granular profiles on electron microscopic examination of extracerebral tissues including skin, muscle, rectal mucosa and blood lymphocytes, and lack of vacuolated lymphocytes. Diagnosis depends on analysis of the CLN7 gene.

CLN8

Late Infantile Variant; Northern Epilepsy Variant; Progressive Epilepsy with Intellectual Disability

The gene CLN8 on chromosome 8p23.3 codes for a transmembrane protein of the endoplasmic reticulum involved in sphingolipid metabolism, which is thought to play a role in cell proliferation during neuronal differentiation and in protection against cell death (Vantaggiato et al. 2009; Haddad et al. 2012). Mutations in CLN8 give rise to two distinct allelic forms of CLN8 with different clinical courses and geographical distribution: a form of progressive epilepsy with intellectual disability known as Northern epilepsy, and a variant of late infantile onset CLN.

The Northern epilepsy, first described in the population of northern Finland by Hirvsnäemi et al. (1994), was recognised by Herva et al. (2000) as a form of CLN with an exceptionally protracted course. It is characterised by an onset between 5 and 10 years of age with frequent tonic–clonic seizures, the frequency of which decreases after puberty, and progressive cognitive deterioration that begins 2−5 years after the onset of epilepsy, and continues during adulthood despite good epilepsy control, leading to intellectual disability by middle age. Unlike the late infantile variant, in Northern epilepsy visual loss is not a prominent feature, there is no myoclonus, and the clinical progression is slower.

Mutations of gene CLN8 were shown to be responsible for late infantile onset CLN in a subset of Turkish patients initially thought to suffer CLN7. The late infantile variant CLN8 has been recognised to have a worldwide distribution (Striano et al. 2007; Reinhardt et al. 2010). The age at onset can be quite early (within the second year of life), with seizures and progressive ataxia, followed by psychomotor regression and myoclonus. The visual system with retinal involvement is always affected, with ERG extinction. Severe involvement of cortical structures is indicated by the giant cortical evoked potentials elicited. The outcome is fatal by the end of the second decade.

The lipopigment patterns observed most often in extracerebral tissues in CLN8 comprise mixed combinations of curvilinear and fingerprint profiles, and, less frequently, granular and rectilinear profiles. No vacuolated lymphocytes are found. Diagnosis is through CLN8 gene analysis.

CLN9

A small number of patients presenting with a juvenile-onset of CLN but without any known gene mutation have been classified as CLN9 (Schulz et al. 2004). Clinical onset is by the age of 4 years with visual loss and seizures followed by progressive cognitive decline and ataxia and death at the end of the second decade. Vacuolated lymphocytes have been described, either empty, or containing electron-dense storage with fingerprint pattern. A brain biopsy from one patient has shown neurons with granular and curvilinear storage. CLN9 is associated with decreased levels of dihydroceramide and decreased dihydroceramide synthase activity in fibroblasts, and the CLN9 protein is thought to be a regulator of dihydroceramide synthase (Schulz et al. 2006).
CLN10

Congenital Classic

CLN10 is the classic form of congenital onset CLN. It is due to homozygous or compound heterozygous mutations in the gene CTSD/CLN10 on chromosome 11p15.5 that codes for the lysosomal enzyme cathepsin D (Siintola et al. 2006; Steinfeld et al. 2006).

First described in 1941 (Norman and Wood 1941), CLN10 is the only CLN where the symptoms are present at birth, in the form of seizures and microcephaly, and death usually occurs within hours or days. There is granular storage material in tissue cells. Confirmation of the diagnosis is based on demonstration of the enzymatic deficiency and a mutation in the CLN10 gene.

Later onset forms of CLN10 have been reported in the literature (Steinfeld et al. 2006) and are thought to be due to partial inactivation of the CTSD gene. These cases present after prior normal development with progressive ataxia, visual loss and cognitive decline, and with a slower course. Interestingly, ultrastructural examination of extracerebral tissues in these cases showed no storage material.

CLN11

CLN11 is caused by homozygous mutations in the GRN/CLN11 gene on chromosome 17q21.31 that codes for progranulin. To date, only one family with CLN11 has been described. Heterozygous mutations in the GRN gene cause frontotemporal lobar degeneration with TDP43-inclusions. Smith et al. (2012) signalled the remarkable phenotypic differences between heterozygous and homozygous GRN mutations, and suggested that progranulin may have a lysosomal function.

The reported family had an adult-onset CLN with rapidly progressive visual loss due to retinal dystrophy, seizures, cerebellar ataxia, and cerebellar atrophy. Cognitive decline may also occur. To date, it is the only adult-onset NCL with retinopathy. Electron microscopic examination of a skin biopsy demonstrated numerous fingerprint profiles. Diagnosis is through GRN/CLN11 gene analysis.

CLN12

CLN12 is caused by homozygous mutations in the ATP13A/CLN12 gene on chromosome 1p36.13 which encodes a lysosomal type 5 ATPase. Only one family with CLN12 has been reported to date (Bras et al. 2012). Homozygous or compound heterozygous mutations in the ATP13A2 gene cause Kufor-Rakeb syndrome, also known as Parkinson disease-9 (PARK9).

The reported family had a juvenile-onset CLN with learning difficulties and, several years later, progressive motor impairment with parkinsonism, spasticity, pseudobulbar syndrome, extrapyramidal symptoms, choreic movements, slow extraocular eye movements and cognitive decline. All patients also developed a peripheral neuropathy and one of them had seizures and myoclonus. No retinal involvement was observed. Lymphocytes showed vacuoles and, ultrastructurally, contained NCL-typical lipopigments, which, on biopsy, were also seen in nerve and skeletal muscle in the form of fingerprint-like profiles. Diagnosis is through ATP13A/CLN12 gene analysis.

CLN13

Kufs Type B

CLN13, also known as Kufs type B, is caused by homozygous or compound heterozygous mutations in the CTSD/CLN13 gene on chromosome 11q13.2 that codes for the lysosomal enzyme cathepsin F.

Only a few cases have been reported to date. It is characterised by adult-onset of progressive cognitive decline and motor dysfunction including tremor, ataxia, dysarthria and pyramidal and extrapyramidal signs, leading to dementia and often early death. Some patients develop seizures. Neurons show abnormal accumulation of autofluorescent material with fingerprint profiles. The pathological features in extracerebral tissues are yet to be reported. Diagnosis is through CTSD/CLN13 gene analysis.

CLN14

Progressive Myoclonic Epilepsy 3, with or without Intracellular Inclusions

Mutations in KCTD7/CLN14, a gene on chromosome 7q11.21 which encodes a member of the potassium channel tetramerisation domain-containing protein family, cause a severe neurodegenerative phenotype characterised by onset of intractable myoclonic seizures before age 2 years and accompanied by developmental regression. The initial description was consistent with a form of progressive myoclonic epilepsy (progressive myoclonic epilepsy 3, with or without intracellular inclusions, EPM3), whereas a later report identified intracellular accumulation of autofluorescent lipopigment storage material, consistent with neuronal ceroid lipofuscinosis (Staropoli et al. 2012).

To date it has been described in three families from Mexico, Morocco and Turkey. It is characterised by infantile onset (9–24 months of age) with progressive myoclonic epilepsy, ataxia, motor and cognitive decline, without retinal involvement. Ultrastructural findings on skin biopsies appear to be variable. Electron microscopy of lymphocytes has shown lysosomal storage material containing fingerprint-like profiles and GRODs. The axons of a myelinated nerve contained vacuole-bound rectilinear profiles. Diagnosis is through CTSF/CLN13 gene analysis.
UNDETERMINED FORMS OF NCLS

In about 10–12% of patients affected with a progressive neurological disorder, whose clinical and neurophysiological features are consistent with a diagnosis of NCL, the gene mutations remain undefined. Most of them are late infantile-onset forms, but later onset cases can also be found. Ultrastructural analysis of peripheral tissues showing the presence of lipopigments and endolysosomal storage with heterogeneous patterns, but rarely containing classic cytosomes. The identification of new informative NCL families is, therefore, necessary in order to recognise new NCL genes.

THE SPINOCEREBELLAR DEGENERATIONS, ATAXIAS, HEREDITARY SPASTIC PARAPLEGIAS AND RELATED CONDITIONS

The terms spinocerebellar degenerations and hereditary ataxias designate a broad category of inherited ataxic disorders, principally involving the cerebellum and its connections, that are characterised by the slow premature death of cells as a consequence of a variety of cellular functional defects. This group of conditions includes a large number of heterogeneous diseases. Most cases of inherited ataxias are caused by repeat expansions in the relevant genes but point mutations also occur. The broad range of mutation types found in inherited ataxias contributes to their complexity. Inheritance patterns include autosomal dominant, autosomal recessive, X-linked and mitochondrial transmission.

In the past 30 years, there has been a remarkable expansion in the understanding of these conditions (Koeppen 2005), so that there are now approximately 40 autosomal recessive spinocerebellar ataxias (SCARs) and numerous dominant SCAs with at least 23 known genes and a further nine identified by locus only. Much is known about the mutated gene products but a good deal less about their precise functional role. Many of the known pathogenetic mechanisms are described by Storey (2014).

From a clinical point of view, it is important to remember that cases of apparent ‘atypical spinocerebellar degeneration’ can result even from an infectious origin (e.g. prion diseases) or from many different metabolic disorders (e.g. glycosylation defects), wherein appropriate metabolic, virological or DNA investigations may permit a more precise diagnosis. Such studies and, where appropriate and available, molecular genetic investigations will often provide the precise diagnosis, permitting better-informed management, appropriate genetic counselling and sometimes prenatal diagnosis and/or (eventually) targeted treatment, although no treatment other than symptomatic is currently available.

Various systems of classification of the spinocerebellar degenerations have been proposed. Classification on the basis of pathological findings has not been convincing because the lesions associated with the same genetic defect are often variable and even the pathological findings in several members of the same family may not be identical. Thus, cases of olivopontocerebellar atrophy can coexist in the same pedigree with cases that do not involve the olivary nuclei! In other SCAs, cases from the same family have been classified under different subgroups. However, a new classification proposed in France and based on mode of inheritance and molecular findings brings about new insights into pathogenic mechanisms and is likely to replace older schemes (Vallat et al. 2016).

For example, in this new classification, conditions currently named spinocerebellar ataxias (SCAs types 1–40 and related conditions) will be referred to as autosomal dominant cerebellar ataxias, the gene (where known) will be attached and their denomination will be by the gene, rather than a number. Thus, SCA1 (AD) will be designated AD-CA-ATXN1 (see Table 10.7). Autosomal recessive SCAs would be included (Table 10.8) and designated as, for example, AR-CA-FRDA for Friedreich Ataxia. In a similar fashion, in regard to the hereditary spastic paraplegias, (Table 10.9) the currently named SPG1, for example, would be abbreviated as XL-SPG-Licam and so forth, and for the spastic ataxias, one such as Spax1 (AD) would be AD-SPAX-VAMPI (see Tables 10.7–10.10). It is anticipated that the new classification will be formally adopted in the near future.

AUTOSOMAL DOMINANT FORMS OF SPINOCEREBELLAR ATAXIAS

The dominant forms of spinocerebellar degeneration comprise a large number of unrelated diseases with many shared clinical features. In assessing cases, it is often impossible, without gene identification, to decide whether one is dealing with a particular condition which has different clinical presentations or with a separate disorder that shares some common clinical and pathological features. In view of this, the traditional nomenclature is retained in the rest of this chapter. Some hereditary ataxias do have features which are strongly suggestive of a particular genotype; for example, visual failure in childhood and young adult cases of spinocerebellar ataxia 7 (SCA7), but for many there is a wide overlap preventing a precise diagnosis of the type on clinical grounds. Where available, the ‘new genetics’ techniques are resolving many of these issues.

Many of these disorders (SCAs 1, 2, 3, 6, 7, 17, denatatorubral + pallidolysian atrophy (DRPLA), and possibly SCA 8) are associated with the presence in the genes of expanded trinucleotide (CAG)n repeats that code for expanded polyglutamine (poly Q) tracts. The proteins bearing these expanded
<table>
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<td>20p13</td>
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<td>20p13</td>
<td>AD-CA-NOP56</td>
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<td>AD-CA-eLOVL5</td>
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<td>14q32.11-q32.12</td>
<td>AD-CA-CCDC88C</td>
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<td>Dentatorubro-pallidolysian atrophy (AD)</td>
<td>ATN1</td>
<td>12p13.31</td>
<td>AD-CA-ATN1</td>
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<td>EA1 (AD)</td>
<td>KCNA1</td>
<td>12p13.32</td>
<td>AD-EA-KCNA1</td>
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<td>CACNB4</td>
<td>2q23.3</td>
<td>AD-EA-CACNB4</td>
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<tr>
<td>EA6 (AD)</td>
<td>SLCA3</td>
<td>5p13.2</td>
<td>AD-EA-SLCA3</td>
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<td>Friedreich's ataxia (AR) (^b)</td>
<td>FRDA/Frataxin</td>
<td>9q13</td>
<td>AR-CA-FRDA or current denomination'</td>
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<td>Ataxia with vitamine E deficiency (AR)</td>
<td>TTPA</td>
<td>8q13.1-13.3</td>
<td>AR-CA-TTPA or current denomination'</td>
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<td>Abetalipoproteinemia (AR)</td>
<td>MTP</td>
<td>4q22-24</td>
<td>AR-CA-MTP or current denomination'</td>
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Continued
### Table 10.7 Proposal for new designations of hereditary cerebellar ataxias (continued)

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<th>Gene</th>
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<th>Proposed denomination</th>
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<tbody>
<tr>
<td>Refsum’s disease (AR)</td>
<td>PHYH</td>
<td>10pter-11.2</td>
<td>AR-CA-PHYH or current denominationa</td>
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<td>No name (AR)</td>
<td>PEX7</td>
<td>6q21-22.2</td>
<td>AR-CA-PEX7</td>
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<td>Late onset Tay-Sachs disease (AR)</td>
<td>HEXA</td>
<td>15q23-24</td>
<td>AR-CA-HEXA or current denominationa</td>
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<tr>
<td>Cerebrotendinous xanthomatosis (AR)</td>
<td>CYP27</td>
<td>2q33-ter</td>
<td>AR-CA-CYP27 or current denominationa</td>
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<td>Mitochondrial recessive ataxia syndrome, SANDO-MIRAS (AR)b</td>
<td>POLG1</td>
<td>15q22-26</td>
<td>AR-CA-POLG1 or current denominationb</td>
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<tr>
<td>Spinocerebellar ataxia with axonal neuropathy (AR)</td>
<td>TDP1</td>
<td>14q31-32</td>
<td>AR-CA-TDP1 or current denominationb</td>
</tr>
<tr>
<td>Ataxia telangiectasia (AR)b</td>
<td>ATM</td>
<td>11q22-23</td>
<td>AR-CA-ATM or current denominationb</td>
</tr>
<tr>
<td>Ataxia telangiectasia-like disorder (AR)</td>
<td>MRE11</td>
<td>11q21</td>
<td>AR-CA-MRE11 or current denominationb</td>
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<tr>
<td>Ataxia with oculomotor apraxia type 1 (AR)</td>
<td>APTX</td>
<td>9p21.1</td>
<td>AR-CA-APTX or current denominationb</td>
</tr>
<tr>
<td>Infantile-onset spinocerebellar ataxia, or IOSCA (AR)</td>
<td>C10orf2</td>
<td>10q24</td>
<td>AR-CA-C10orf2 or current denominationb</td>
</tr>
<tr>
<td>Cayman ataxia (AR)</td>
<td>ATCAY</td>
<td>19p13.3</td>
<td>AR-CA-ATCAY or current denominationb</td>
</tr>
<tr>
<td>Marinesco-Sjögren syndrome (AR)</td>
<td>SIL1</td>
<td>5q31</td>
<td>AR-CA-SIL1 or current denominationb</td>
</tr>
<tr>
<td>Ataxia of Charlevoix-Saguenay (ARSACS)</td>
<td>SACS</td>
<td>13q11</td>
<td>AR-CA-SACS or current denominationb</td>
</tr>
<tr>
<td>SCAR1 (AR)</td>
<td>SETX</td>
<td>9q34.13</td>
<td>AR-CA-SETX</td>
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a Our suggestions may not be strictly applied to all genetic disorders as some current designations may be considered well-recognised, universally used, and not too complex for practical use.
b The most frequent types.

AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CA, hereditary cerebellar ataxia; CMT, Charcot–Marie–Tooth disease; dHMN, distal hereditary motor neuropathy; EA, episodic ataxia; MIRAS, mitochondrial recessive ataxia syndrome; mit, mitochondrial transmission; MP, myopathic facies; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SCA, spinocerebellar ataxia; SCAR, spinocerebellar ataxia autosomal recessive; SP, spastic paraparesis; SPG, hereditary spastic paraplegia; XL, X-linked.

### Table 10.8 The recessive hereditary ataxias

<table>
<thead>
<tr>
<th>Name of condition</th>
<th>Gene product</th>
<th>Special features</th>
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<tbody>
<tr>
<td>Freidreich ataxia (FA)</td>
<td>Frataxin</td>
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<tr>
<td>Early-onset ataxia with retained tendon reflexes (FARR)</td>
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<tr>
<td>Ataxia with isolated vitamin E deficiency (AVED)</td>
<td>TTPA</td>
<td>Low vitamin E levels</td>
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<tr>
<td>Ataxia with coenzyme Q10 deficiency</td>
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<td></td>
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<tr>
<td>Ataxia with ocular motor apraxia (AOA type 1)</td>
<td>Aprataxin</td>
<td>Low serum albumin</td>
</tr>
<tr>
<td>Ataxia with ocular motor apraxia (AOA type 2)</td>
<td>Senataxin</td>
<td></td>
</tr>
<tr>
<td>Early-onset ataxia with hypogonadism and retinal dystrophy (Boucher-Neuhauser syndrome)</td>
<td>Phospholipid esterase protein</td>
<td>Early-onset ataxia and hypogonadism plus chorioretinal dystrophy + or – hypersegmented neutrophils</td>
</tr>
<tr>
<td>Early-onset ataxia with cataracts (Marinesco-Sjögren)</td>
<td>Nucleotide exchange factor for BiP chaperone</td>
<td>Cataracts, ataxia, myopathy, ID</td>
</tr>
<tr>
<td>Early-onset ataxia with deafness and optic atrophy (optico-cochleo-dentate syndrome)</td>
<td>Due to D-bifunctional protein deficiency (peroxisomal)</td>
<td>Ataxia, deafness, optic atrophy</td>
</tr>
<tr>
<td>Infantile early-onset spinocerebellar ataxia (IOSCA)</td>
<td>Twinkle</td>
<td>Mostly seen in Finland</td>
</tr>
<tr>
<td>Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)</td>
<td>Sacsin</td>
<td>Mostly seen in Quebec but in Europe, Japan and the Middle East also</td>
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Table 10.9 Proposal for new designations of hereditary spastic paraplegias

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<tr>
<th>Current denomination</th>
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<th>Chromosome</th>
<th>Proposed denomination</th>
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<tbody>
<tr>
<td>SPG1 (XL)</td>
<td>L1CAM</td>
<td>Xq28</td>
<td>XL-SPG-L1CAM</td>
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<tr>
<td>SPG2 (XL)</td>
<td>PLP1</td>
<td>Xq22.2</td>
<td>XL-SPG-PLP1</td>
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<td>SPG3 (AD)</td>
<td>ATL1</td>
<td>14q22.1</td>
<td>AD-SPG-ATL1</td>
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<tr>
<td>SPG3A (AR)</td>
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<td></td>
<td>AR-SPG-ATL1</td>
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<tr>
<td>SPG4 (AD) a</td>
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<td></td>
<td>AR-SPG-SPAST</td>
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<td>8q12.3</td>
<td>AR-SPG-CYP7B1</td>
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<td>SPG6 (AD)</td>
<td>NIPA1</td>
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<td>AD-SPG-NIPA1</td>
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<td>SPG7 (AR) a</td>
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<td>16q24.3</td>
<td>AR-SPG-SPG7</td>
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<td>15q21.1</td>
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<td>RTN2</td>
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<td>(AD-SPG- KIF1C)?</td>
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<td>RAB3GAP2</td>
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<td>SPG70 (AR)</td>
<td>MAR5</td>
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<td>ZFR</td>
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</tr>
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</tr>
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<td>CCT5</td>
<td>5p15.2</td>
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<tr>
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<td>AR-SPG-LYST</td>
</tr>
<tr>
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<td>19q13.1</td>
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</tr>
<tr>
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<td>Mt-CO3</td>
<td>Mitochondrial DMA</td>
<td>mit-SPG-CO3</td>
</tr>
<tr>
<td>No name (mit)</td>
<td>Mt-TI</td>
<td>Mitochondrial DMA</td>
<td>mit-SPG-TI</td>
</tr>
<tr>
<td>No name (mit)</td>
<td>Mt-ATP6</td>
<td>Mitochondrial DMA</td>
<td>mit-SPG-ATP6</td>
</tr>
</tbody>
</table>

Continued
poly Q tracts accumulate in the nucleus and/or cytoplasm of neurons in the form of inclusions, although these are probably markers rather than being pathogenic. Poly Q tracts may interfere with intracellular traffic by jamming metabolic pathways (Gunawardena and Goldstein 2005) or result in a gain-of-function toxicity (van de Warrenburg et al. 2005). In other types, such as SCAs 10, 12 and 31, the repeats are not translated and not associated with polyglutamine inclusions. Their mechanisms of action are various and may include inhibition of gene translation (Everett and Wood 2004; Dueñas et al. 2006; Storey 2014), while others often remain unclear.

SCAs are mostly disorders of adults and only a few of them are encountered with any frequency in children, usually as a result of the phenomenon of anticipation; that is, earlier onset in subsequent generations, correlating with intergenerational expansion of the CAG tract. Anticipation is more prominent when the condition is inherited from the male parent, and is more likely to be extreme in SCA 7, where there are no stabilising non-CAG trinucleotides, or in SCA2, where interposed stabilising CAA trinucleotides are lost.

The SCAs can be sub-divided based on the proposed pathogenetic mechanism into three subclasses: subclass 1 includes SCAs caused by CAG repeat expansions such as SCA1-SCA3, SCA17 and DRPLA; subclass 2 includes trinucleotide or other repeat expansions that fall outside the protein-coding regions of the disease gene and includes SCAs 10, 12 and 31. Subclass 3 contains disorders caused by specific gene deletions, missense mutations and nonsense mutations, and includes SCAs 5, 11, 13, 14, SCA15/16, SCA27 and SCA28.

Diagnosis is based on clinical history, physical examination, molecular genetic testing and exclusion of other diseases (Whaley et al. 2011). MRI showing marked cerebellar atrophy (involving primarily the vermis) and brainstem atrophy, particularly of the pons whose normal bulge is classically no longer visible (Wüllner et al. 1993; Döhlinger et al. 2008). The degree of atrophy is typically greatest in SCA2, followed by SCA1 and then SCA3.

The global prevalence of these conditions is not precisely known but an overall combined prevalence of about 6/100 000 is a fair approximation. Population prevalence studies of hereditary ataxias have been carried out in Norway (5.2/100 000), Italy (9.3/100 000), and Singapore (3.7 families/100 000). Founder effects no doubt contribute to the variable prevalence between populations. Broadly speaking, in Western countries, the most common type is SCA3 (Machado–Joseph disease), followed by SCA2, SCA6, SCA1 and SCA8 (Whaley et al. 2011). Even in tertiary centres, these conditions are seen rather infrequently in children.

In the Australian state of New South Wales where DNA on 900 persons of all ages has been examined for SCAs 1, 2, 3, 6 and 7, only two cases aged under 16 years have been discovered, a male aged 11 with ataxia, vision problems and a relevant family history who was positive (~51 repeats) for SCA7 and a boy aged 15 with ataxia and a positive family history who had SCA3 (~74 repeats) (Nicolson and Aziz, personal communication 2014). Two siblings in a Sydney family with early-onset SCA6 studied in another laboratory are also known. SCA3 is also present in isolated aboriginal communities in Northern Australia.

Onset in children aged less than 1 year has been recorded in SCA2 (Di Fabio et al. 2012), SCA7 and DRPLA and as early as age 4, 5, 1 and 3 years respectively in SCA1, SCA3, SCA6 and SCA17.

### Table 10.9 Proposal for new designations of hereditary spastic paraplegias (continued)

<table>
<thead>
<tr>
<th>Current denomination</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Proposed denomination</th>
</tr>
</thead>
<tbody>
<tr>
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<td>9p13.3</td>
<td>AD-SPG-VCP</td>
</tr>
<tr>
<td>No name (AR)</td>
<td>RNASEH2B</td>
<td>13q14.3</td>
<td>AR-SPG-RNASEH2B</td>
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<tr>
<td>No name (AR)</td>
<td>SACS</td>
<td>13q11</td>
<td>AR-SPG-SACS</td>
</tr>
<tr>
<td>No name (AR)</td>
<td>TECPR2</td>
<td>14q32.31</td>
<td>AR-SPG-TECPR2</td>
</tr>
<tr>
<td>No name (AR)</td>
<td>TUBB4A</td>
<td>19p13.3</td>
<td>AR-SPG-TUBB4A</td>
</tr>
</tbody>
</table>

a The most frequent types.

AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot–Marie–Tooth disease; dHMN, distal hereditary motor neuropathy; HSAN, hereditary sensory and autonomic neuropathy; mit, mitochondrial transmission; SPG, hereditary spastic paraplegia; XL, X-linked.

### Table 10.10 Percentage frequency of major clinical features of Friedreich ataxia from three studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>99</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>97</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Absent lower limb reflexes</td>
<td>99</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>79</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>Pes cavus</td>
<td>55</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>Swallowing disturbance</td>
<td>–</td>
<td>27</td>
<td>–</td>
</tr>
<tr>
<td>Sphincter disturbance</td>
<td>–</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Reduced vision</td>
<td>18</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>8</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Cardiomyopathy on echocardiogram</td>
<td>–</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Diabetes/abnormal glucose tolerance</td>
<td>10</td>
<td>32</td>
<td>8</td>
</tr>
</tbody>
</table>
The types that are more often observed in children – SCA1, SCA2, SCA3, SCA7, SCA17 and DRPLA (dentatorubral–pallidolysian atrophy) – are listed in Table 10.7 (Vallat et al. 2016) and will be briefly described below. SCAs which are largely confined to specific ethnic groups (such as SCA4 in Utah, SCA10 in Mexico and southern Brazil) or to small, even notable kindreds (such as SCA5 in members of Abraham Lincoln’s family, with a mutation in the gene for spectrin (Ikeda et al. 2006]) will not be discussed further.

**SPINOCEREBELLAR ATAXIA TYPE 1**

SCA1 is caused by mutations in the ATXN1 gene which are associated with expansion of its CAG repeats. The normal gene contains 6–44 CAG repeats. If, however, the CAG repeats in the 36–44 range are not interrupted by 1–3 CAG trinucleotide repeats, they may be in the ‘mutable normal’ range (36–38 CAG repeats) where there is a risk of anticipation in following generations or, if there are 39–44 uninterrupted CAG repeats, pathogenic to the carrier. It used to be thought that the expanded polyglutamines, encoded as a result of the CAG expansion, caused misfolding of mutant ataxin-1 leading to insoluble aggregates which accumulated and interfered with cellular protein refolding and subsequent proteolysis (Cummings et al. 1999). However, there is evidence for host protein specificity in SCA1, in that the expanded poly Q tract alters the interaction of ataxin-1 with a number of its protein partners – such as RBM17 and Capicua – in the control of RNA transcription and splicing (Ort 2012).

SCA1 has an estimated incidence of one to two per 100,000 in Western countries but there is marked variation in its frequency worldwide. Onset with symptoms and signs of cerebellar disease is typically in the third or fourth decade but childhood cases with onset as young as 4 years develop, in addition, severe brainstem dysfunction which progresses rapidly, leading to death within 4–8 years of symptom onset (Zoghbi et al. 1988). In adult-onset SCA1, the duration of illness from onset to death ranges from 10 to 30 years. In addition to the cerebellar symptoms, affected individuals may display spasticity with brisk deep tendon reflexes, hypermetric saccades, and sometimes nystagmus. The latter occurs in only about 10–25% of cases and thus is a point of distinction from SCA3 and SCA6. It may appear in the early stages of disease but later disappears. As the disease progresses the saccadic velocity slows, and an up-gaze palsy develops. Optic atrophy and variable degrees of ophthalmoplegia may be detected in some individuals.

Later, muscle wasting, hyporeflexia and impairment of proprioceptive and vibration sensation may supervene. Neurophysiological studies indicate a neuronopathy (van de Warrenburg et al. 2004). Dysphagia and extrapyramidal signs such as chorea and dystonia as well as cognitive decline may occur. Affected individuals eventually develop respiratory failure, which is the main cause of death.

**SPINOCEREBELLAR ATAXIA TYPE 2**

SCA 2 is due to a (CAG)n repeat expansion in the ATXN2 gene, encoding ataxin 2 (Vinthe-Jensen et al. 2013). This cytoplasmic protein is involved in the regulation of mRNA translation, through its interactions with the polyalanine binding protein (PABP) and ataxin-2-binding protein. Interestingly, intermediate expansions of ATXN2 of 27–33 repeats, often smaller than the 32 repeat threshold for SCA2, have emerged as an important genetic risk factor for ALS.

SCA 2 is particularly common in southern Italy and Cuba, as well as in India where it was first described phenotypically by Wadia and Swami (1971). The onset is typically in middle age, although it is subject to extreme anticipation, and infantile cases are therefore well-described. It is characterised by very slow, almost viscous saccades, with progressive sensory loss and areflexia overtaking early pyramidal signs. Cognitive impairment, beyond the usual mild dysexecutive syndrome seen in cerebellar ataxias generally as part of the cerebellar cognitive affective syndrome, is often a feature. Some patients, particularly those of East Asian descent, may present with dopa-responsive parkinsonism (Gwinn-Hardy et al. 2000).

**SPINOCEREBELLAR ATAXIA TYPE 3 (MACHADO–JOSEPH DISEASE)**

Mutations at the SCA3 locus are the cause of Machado–Joseph disease (Dürr et al. 1996b), the most common type of SCA in Western Europe although uncommon in Italy, the UK and Slavic countries. Like SCA1, it is also due to an abnormal trinucleotide expansion in ATXN3 containing 52–86 CAG repeats. The disease is more common among persons originating from the Azores Islands and Portugal, and their descendants. Like SCA1, it is also due to an abnormal trinucleotide expansion in ATXN3 containing 52–86 CAG repeats. Machado–Joseph disease is very uncommon in young children. Onset is usually in the third or fourth decade with a mean survival of 20–30 years.

Before the discovery of the ATXN3 gene mutation, phenotypic studies had recognised three sub-phenotypes, emphasising the degree of phenotypic heterogeneity. Type I, with the earliest onset (usually 10–30 years), showed rapid progression with akinsia and rigidity or dystonia, pyramidal features, and variably, cerebellar ataxia. The extrapyramidal features are often responsive to dopaminergic agonists, which may cause confusion with dopa-responsive dystonia or parkinsonism. Type II, with an intermediate age at onset of 20–50 years, was characterised by spasticity and hyper-reflexia associated with cerebellar ataxia so that, in some families, the hyper-reflexia and upper motor neuron signs may suggest hereditary spastic paraplegia. Type III, of later onset (over 40 years), was typified by predominant cerebellar ataxia with significant peripheral wasting and generalised areflexia due to peripheral neuropathy or neuronopathy, the lower motor neuron involvement causing fasciculations and bulbar palsy. Ataxia gradually progresses and...
dysarthria may occur. Some patients may manifest predominantly ocular signs, including nystagmus and sometimes progressing to ophthalmoplegia, and others a pure ataxic syndrome, while yet others have a mid-life onset with parkinsonism.

Brain imaging studies typically reveal pontocerebellar atrophy with enlargement of the fourth ventricle, corresponding with dentate nucleus atrophy.

**SPINOCEREBELLAR ATAXIA TYPE 6**

SCA type 6 is caused by mutations involving CAG repeats on the calcium channel-encoding CACNA1A gene on chromosome 19. Missense and nonsense mutations at the same site are reported to cause familial hemiplegic migraine and episodic ataxia type 2, and the phenotypes for all three disorders may sometimes overlap. Downbeating nystagmus is a frequent feature. SCA 6 has very rarely been reported in children. Most cases present in adulthood (age range 14–73 years). The following case history describes typical early features in two siblings who are among the youngest patients reported to date. Although SCA6 is usually regarded as a ‘pure’ ataxia, other manifestations can include hyper-reflexia and extensor plantar responses, dystonia and blepharospasm. Dysphagia can be serious. Cognitive functions are usually preserved. Increased severity in pregnancy has been reported. Life span is not shortened, at least in typical cases.

Neuropathological studies have revealed degeneration of Purkinje and granule cells.

**CASE REPORT 1 (COURTESY DR C TROEDSON, SYDNEY)**

Two sisters presented at the ages of 14 and 32 months with frequent falls. The older child had a suspected esotropia with subtle abnormalities of upward gaze. She seemed to fall over more often when wearing glasses and resisted wearing them. Nystagmus was subsequently detected and hypometric saccades were noted at age 4. The younger sister had similar ocular findings, considered to be consistent with oculomotor apraxia but neither child had definite cerebellar signs on neurological examination. MRI showed mild cerebellar atrophy.

The mother, who also suffered from migraine without hemiplegia, was known to have a long history of ataxia and dystonia with a significant deterioration after her pregnancies (and a motor vehicle accident). Her MRI revealed diffuse cerebellar atrophy.

DNA studies on the mother and both daughters revealed the presence of a missense mutation in exon 25 of the CACNA1A gene in all three, indicating a diagnosis of SCA 6.

**SPINOCEREBELLAR ATAXIA TYPE 7**

SCA type 7 condition was previously described as Olivopontocerebellar atrophy type 3 (OPCA3) and autosomal dominant cerebellar ataxia type 2 (ADCA2). The gene SCA7 maps to 3p12–p21.1 (Benomar et al. 1995) and codes for the protein ataxin 7. Inclusions within the cell nuclei contain both ataxin and ubiquitin (Ansorge et al. 2004). Ataxin 7 itself is a component of transcription regulation complexes, including the retinal transcription factor CRX, and these functions are perturbed by the poly Q expansion. It also appears that non-cell autonomous toxicity may be involved in SCA 7 pathogenesis, with impaired glutamate uptake by Bergmann glia implicated (Garden and La Spada 2008).

The picture in adults is that of a macular degeneration with progressive cerebellar ataxia. The macular degeneration may long remain isolated. Cases under 50 years tend to present with visual symptoms first, and those over 50 with ataxic symptoms first.

A remarkable degree of anticipation can be observed in affected lineages, and a very early onset (from age 6 months) may occur. Benton et al. reported a child with early hypotonia, dysphagia causing failure to thrive, congestive heart failure, cerebellar atrophy and inability to track objects visually. Other similar infantile onset cases are described. Such cases run a rapidly fatal course (see Case Report 2).

**CASE REPORT 2 (COURTESY DR P GRATAN-SMITH, SYDNEY)**

A 23-month-old girl presented with progressive ataxia. There had been no problems in the pregnancy or neonatal period.

The mother reported that the infant may have been ataxic from around the age of 12 months. At 21 months, an esotropia developed and at 23 months she had not yet begun talking. On examination at 23 months, her head circumference was on the 50th centile. There was a pigmentary retinopathy but normal pupillary response to light.

She could reach out unsteadily with either hand to grasp objects and required assistance to walk because of ataxia and head titubation. Tone, strength and reflexes were normal.

She continued to deteriorate and when reviewed at 30 months, although her comprehension seemed intact, she was no longer able to roll, sit, cruise or crawl. She had become grossly ataxic and adopted a chin-down posture. Both maculae were deeply pigmented and there was diffuse background retinopathy. The optic discs were pale and the retinal vessels were attenuated. Eye movement testing revealed bilateral limitation of abduction. She was generally hypotonic, weak and had poor muscle bulk. Her deep tendon reflexes were now absent.

Normal investigations included full blood count (no ancytocytes), electrolytes, liver function tests, serum ammonia and lactate, immunoglobulins, alpha-fetoprotein, transferrin isofoms, 7-dehydrocholesterol, lysosomal enzymes, long chain fatty acid ratios, cholesterol, triglycerides, vitamin E, urine amino and organic acid screens, urine heavy metal screen and CSF lactate and glucose. An ECG and EEG were both normal. The mitochondrial DNA mutations T8993G and T8993C were absent in muscle. Respiratory chain enzymes in the liver and muscle were normal. No frataxin expansion was seen. An ERG showed a flat scotopic response and reduced photopic response, indicating widespread photoreceptor dysfunction. Nerve conduction studies showed absent sensory action potentials but normal motor responses. Sural nerve biopsy demonstrated an axonal neuropathy.
There was progressive cerebellar and cerebral atrophy on serial MRI scans. She died at home aged 3 years and 3 months. No post mortem was performed. The father, aged 33 years, had a 4–5 year history of blurred vision which had become worse in the preceding 2 years. He was seen by an ophthalmologist who found his visual acuity to be 6/60 in both eyes. He had also been ataxic for approximately 2 years and when examined by a neurologist was found to have a broad-based ataxic gait but no limb ataxia. DNA testing confirmed the presence of SCA7 in the father and the fetus in a subsequent pregnancy.

Pathologically, there is atrophy of the dentate-rubral efferent system as in Ramsay Hunt syndrome, associated with nonspecific pallidoluysian atrophy. Intranuclear inclusions are seen in neurons as well as glia. White matter changes may also be seen.

The disease is uncommon outside Japan but cases have been reported in China, Europe, South America and in African-Americans (Licht and Lynch 2002; Wardle et al. 2009), so it should be thought of in cases of childhood myoclonic epilepsy as well as of ataxia.

**SPINOCEREBELLAR ATAXIA TYPE 17**

SCA type 17 (SCA17) is caused by mutations of the TBP gene on chromosome 6q27 which result in CAG repeat expansions in the TATA-box binding protein (a transcription initiation factor). It is characterised by predominant ataxia, associated with parkinsonism and involuntary movements, including chorea and dystonia. Psychiatric symptoms, dementia, pyramidal signs and rigidity are common and may be the presenting feature, especially with smaller repeat sizes (43–50), a clue being the concomitant cerebral and cerebellar atrophy seen on MRI.

The onset may occur at up to 55 years or, on occasion, as young as 3 years, due to anticipation. Such anticipation is, however, rare compared with that seen in the other poly Q disorders (especially SCAs 2 and 7, and DRPLA), probably due to the presence of CAA intrusions (also coding for glutamine) within the CAG repeat sequence.

**DENTATORUBRAL–PALLIDOLUYSIAN ATROPHY**

Dentatorubral–pallidoluysian atrophy (DRPLA) is a condition associated with an expansion of a CAG trinucleotide repeat and has many characteristics of the autosomal dominant SCAs but is usually treated separately. It is due to mutations of repeat and has many characteristics of the autosomal dominant ataxia associated with an expansion of a CAG trinucleotide

**AUTOSOMAL RECESSIVE FORMS OF SPINOCEREBELLAR ATAXIAS**

Over 40 autosomal recessive hereditary ataxias (SCARS) are now recognised, of which Friedreich ataxia (FRDA) is by far the most frequent. Table 10.8 lists the commoner entities and those for which specific therapy is available.

In the following section, FRDA will be discussed in detail including its differential diagnosis and followed by summaries of the more distinctive or treatable SCARS.

**FRIEDREICH ATAXIA**

Although virtually absent from East Asian and sub-Saharan African populations, FRDA is by far the most common and most important type of degenerative ataxia seen in childhood in most Western countries. Its overall prevalence is about one in 29,000 Caucasians. The average reported age at onset was between 10 and 15 years (Harding 1993; Dürr et al. 1996a; Delatycki 1999) but in family studies, careful examination of some affected children may detect signs before the age of 3 years.

**GENETICS**

The gene for Friedreich ataxia (FXN, previously known as X25), found at 9q13, includes a repeat GAA sequence in intron 1 that is expanded from the 5 to 33 repeats in normal individuals to 66–1700 repeats in typically affected patients with FRDA. Mutale normal alleles, which contain 34–66 pure (uninterrupted) GAA triplet repeats, are not associated with FRDA but may expand during intergenerational transmission, resulting in disease-causing alleles in the offspring.

Up to 94% of patients with typical FRDA are homozygous for the GAA expansion, although the length of the repeat is usually unequal on each of the pair of chromosomes (Dürr et al. 1996a). A few have only one allele with an expanded sequence, with an inactivating point mutation or deletion at the homologous allele occurring in such cases (Delatycki and Corben 2012). If there is not at least one expanded triplet repeat allele, there is no point sequencing the genes for point mutations, as the homozygous state for point mutations is presumably lethal in the embryo.

The size of the expanded GAA repeat (particularly the shorter expanded allele, GAA1) partly explains the variability
in symptom onset, severity, and disease progression seen in FRDA. GAA1 length has an inverse correlation with age at symptom onset, and time from symptom onset to wheelchair dependency. However, this is thought to explain only about 40% of the variability (Mateo et al. 2004). GAA1 size also correlates with the presence of cardiomyopathy and scoliosis (Dürr et al. 1996a; Delatycki 1999). As expected, age at symptom onset also correlates with disease progression (Montermini et al. 1997).

Up to 25% of patients with FRDA who are homozygous for the GAA triplet repeat expansion have ‘atypical’ FRDA as they vary from the classic FRDA phenotype originally described by Harding (1993) (Dürr et al. 1996a; Lamont 1997). These include later onset FRDA (onset after 25 years of age) and FRDA with retained reflexes (FARR). It is better to consider these phenotypes as being a spectrum of disease severity, with the size of GAA1 accounting for at least some of these differences. Those with later onset FRDA have lower rates of skeletal deformity, areflexia, and cardiomyopathy (Bhidayasiri et al. 2005; La Pena et al. 2008).

The normal gene product is a mitochondrial protein, frataxin, which binds iron and is required for the synthesis both of iron-sulphur clusters and of enzymes in the respiratory chain. Frataxin deficiency results in secondary deficiency of iron-sulphur cluster-containing enzymes, mislocalisation of cellular iron, and increased sensitivity to oxidative stress (Bidichandani and Delatycki 2012).

A second gene on chromosome 9p23–p11 which had been suggested to account for rare cases clinically indistinguishable from classic FRDA (referred to as Friedreich 2) (Christodoulou et al. 2001) has now been shown to be the cause of ataxia with ocular motor apraxia (AOA type 1).

The main clinical manifestations of FRDA are summarised in Table 10.10. They were determined in three studies including 115 patients from 90 families studied by Harding (1981a) and two more recent series based on cases with gene confirmation (Dürr et al. 1996a; Delatycki et al. 1999).

The onset of ataxia is mostly between 5 and 16 years with a few cases manifesting frequent stumbles and falls as early as 4–5 years of age. At presentation, children with FRDA can rarely stand on one leg for more than a few seconds. They can rarely perform smooth tandem walking. Pes cavus, or at times pes planus, is also an early sign. In persons with Charcot–Marie–Tooth neuropathy, foot strength is usually worse than in FRDA with visually similar cases of pes cavus. Distal wasting is present in almost half the cases. Involvement of the upper limbs with resulting clumsiness is seen early in only 25% of cases. Scoliosis, tremor and cardiac symptoms are rarely the first manifestation, but they eventually develop, especially in those with early onset. Examination showing absent deep tendon reflexes in the lower limbs in 70–95% of cases but extensor planar responses are very common and sometimes exaggerated knee and ankle jerks are found in the legs (FARR). Dysarthria and loss of joint position and vibration sense appear later but are eventually almost constant findings. Nystagmus is frequent (20–50% of cases). Nystagmus is frequent (20–50% of cases), and square wave jerks (a sign of fixation instability) are seen in most patients. Other ocular findings include macroscandacocidal oscillations (ocular flutter), dysmetria, abnormalities of saccades with slow broken pursuit, unstable fixation and impaired vestibular-ocular reflexes (Fahey et al. 2008). Optic atrophy occurs in up to 30% of patients but is rarely obvious before puberty. Sudden loss of central vision with or without recovery may occur (Fortuna et al. 2009). Sensorineural hearing loss occurs in 10–15% of patients, but speech perception (particularly in background noise) is far more common and impacts everyday listening circumstances. Neurogenic bladder symptoms occur in up to 50% of individuals with FRDA. Sleep disordered breathing has been shown to be more common in FRDA compared to the general population (Corben 2013).

Intelligence has been thought to be unaffected but recent reports have documented impairment in verbal fluency, visuoconstructive and visuoperceptual capacity, and motor and cognitive reaction times. Mantovan el al. (2006) concluded that the cognitive profile of individuals with FRDA is characterised by concrete thinking, poor capacity in concept formation and visuospatial reasoning with reduced speed of information processing. Difficulties with attention and working memory have also been demonstrated.

Cardiac involvement is found by electrocardiogram (ECG) in two-thirds of cases, or even more when ECGs and echo-cardiography are performed systematically. In consequence, the most specific clue for the diagnosis of FRDA in an ataxic patient is the presence of cardiomyopathy, T-wave changes and abnormalities of the ST segment are early signs. Echocardiography typically reveals asymmetric septal and concentric left ventricular hypertrophy. The repolarisation abnormalities (T-wave changes) on ECG seem to be more sensitive to cardiac involvement than echocardiography.

It is thought that progression from a hypertrophic to dilated cardiomyopathy occurs over time. However, the natural history of cardiac disease in FRDA is not well understood, and disease duration and neurological disability do not correlate with the severity of cardiomyopathy. Cardiac failure is seldom a presenting feature although occasional cases of unexpected sudden death occur, even in childhood. Progressive cardiac failure, often asymptomatic because of the patient’s neurologically enforced lack of mobility, or arrhythmias with atrial fibrillation eventually develop and over half the patients die of cardiac failure (Leone et al. 1988).

Diabetes mellitus is a further complication in 8–32% of patients. It tends to be associated with optic atrophy. Diabetic coma is sometimes the cause of death.

In the large study conducted by Harding in the early 1980s, the neurological course was slow but progressive. On average, patients lost the ability to walk by 25 years of age after a median illness duration of 15.5 years. The average age at death was 37 years (Harding 1981a). In a more recent study (Tsou et al. 2011), the mean age of death was 36.5 years but
survival into the sixth, seventh and even the ninth decades has been documented. The most common cause of death was cardiac (38/61), with the remainder (17/61) being non-cardiac (most commonly pneumonia) or of unknown cause (6/61).

**Pathological findings in FRDA**

The main pathological lesion is a degenerative process affecting the axons of the long ascending and descending tracts of the spinal cord and the large sensory fibres of peripheral nerves and posterior root ganglia (Ouvrier et al. 1982; Saïd et al. 1986). Loss of nerve fibres has also been documented in the optic pathways. In the brain, the cerebellum itself is mildly affected in childhood but later its white matter is gliotic and the superior cerebellar peduncles degenerate. The dentate nuclei are usually affected. In some cases the cochlear and vestibular nuclei are also affected. There is loss of cells in the gracile and cuneate nuclei and of pyramidal cells in the motor cortex. The heart is enlarged, and in over half the cases, there is a hypertrophic cardiomyopathy with muscle fibre necrosis and fibrosis, mainly involving the left ventricle.

**Investigations — Neuroimaging**

MRI is often normal in the early stages of FRDA. Indeed, the presence of significant cerebellar atrophy on MRI at presentation makes FRDA less likely. With advanced disease, atrophy of the cervical spinal cord and cerebellum may be observed (Bhidayasiri et al. 2005). Atrophy of the superior cerebellar peduncle, the main outflow tract of the dentate nucleus, may also be seen (Akhlaghi et al. 2011). Diffusion weighted imaging showing evidence of a pathological process also involving the optic radiation, independent of optic nerve damage (Fortuna et al. 2009).

**Investigations — Clinical Neurophysiology**

Motor conduction velocity is typically slightly decreased in most cases. Sensory nerve action potentials are markedly reduced or absent. A mild reduction in motor conduction velocity in combination with preserved or mildly reduced compound muscle action potentials is present in some individuals. Denervation changes are also evident on EMG in some cases (Ackroyd et al. 1984; Caruso et al. 1987; De Michele et al. 1996). Somatosensory evoked potentials are absent or markedly reduced. Visual evoked potentials are diminished or delayed (in about half of patients) (Fortuna et al. 2009).

The differential diagnosis and management of FRDA and other inherited ataxias are discussed after the other inherited ataxias.

**Other Autosomal Recessive Cerebellar Ataxias**

These are mostly rare conditions which have been divided into three subgroups:

1. Those in which the available data point to involvement of the spinocerebellar system and a sensory neuropathy;
2. Those in which sensorimotor neuropathy is a major feature;
3. Those in which there is apparently pure cerebellar involvement (Koenig 2003).

The main disorders are listed in Table 10.7. Detailed information on these and other even rarer conditions is found in Bolshhauser and Schmahmann (2012). A few that are of special interest are discussed below.

Ataxia with isolated vitamin E deficiency (AVED) is of therapeutic interest as treatment may stabilise or even improve the clinical manifestations (Roubertie et al. 2003; Mariotti et al. 2004). However, treatment may not totally prevent the late appearance of new neurological signs, despite the initial and persistent good effect on the neuropathy. Abetalipoproteinemia and hypobetalipoproteinemia, many of the manifestations of which result from vitamin E deficiency, are discussed in Chapter 9.

**Ataxia with Coenzyme Q10 Deficiency**

Deficiency of coenzyme Q10 presents in protean ways including enccephalomyopathy, severe infantile multisystemic disease, nephropathy, cerebellar ataxia and isolated myopathy. Early manifestations of the ataxic form include hypotonia, developmental delay, clumsiness and frequent falls. Other manifestations such as dysarthria, epilepsy, nystagmus and ophthalmoplegia, pyramidal signs and a sensorimotor neuropathy with distal weakness, scoliosis and cognitive impairment may emerge. Muscle levels of CoQ10 are low but serum levels may be normal. MRI scans reveal diffuse cerebellar atrophy. Mutations of several genes in CoQ production (COQ4 and, as most prevalent in the ataxic form, ADCK3) have been described (Lagier-Tourenne et al. 2008; Salviati et al. 2012). Treatment may halt progression but is ineffective in some patients (Quinzii et al. 2005).

Infantile early-onset spinocerebellar ataxia (IOSCA) is linked to mutations of the C10orf2 gene on chromosome 10. The disease has been reported mostly from Finland as O-HAHA syndrome with ophthalmoplegia, hypogonadism, ataxia, hypotonias and athetosis being the strikingly suggestive clinical features. Onset is neonatal or in the first two years (Lonnqvist et al. 1998). The course is progressive. Sensorineural deafness is a prominent symptom and may have an abrupt onset, often after the age of 3 years with resulting loss of language.

**Spinocerebellar Ataxias and Hypogonadotropic Hypogonadism**

Boucher–Neuhauser syndrome (BNHS) is caused by mutations in the PNPLA6 gene and is characterised by hypogonadotropic hypogonadism in association with a spinocerebellar syndrome and the presence of a choroidal dystrophy or pigmentary retinopathy. A clinically similar condition, the Gordon Holmes syndrome, is accompanied by hyper-reflexia. In nine patients from four unrelated families with BNHS studied
by Synofzik and colleagues (2014), the age at onset was variable, but most patients developed one or more symptoms in the first decade of life. A patient from a fifth family who did not have chorioretinopathy also carried a PNPLA6 mutation. The authors concluded that BNHS is part of a spectrum of neurodegenerative diseases associated with mutations in the PNPLA6 gene that also includes hereditary spastic paraplegia type 39. The PNPLA6 gene encodes an enzyme that catalyses the de-esterification of membrane phosphatidylcholine into fatty acids and glycerophosphocholine.

The constellation of ataxia and hypogonadism can also be present in other conditions, such as 4H syndrome (MIM #607694 and 614381), Marinesco–SJögren syndrome, galactosaemia, CDG syndrome, STUB1 mutations (MIM #615768) and RNF216/OTUD4 mutations (MIM #212840).

A very rare disease is the optico-cochleo-dentate syndrome, of which the earlier-onset type with hypotonia from birth, blindness, deafness and early death has been recently shown to be a peroxisomal disorder (Schröder et al. 2004). See MIM #261515 for peroxisomal D-bifunctional protein deficiency. Many progressive conditions can eventually cause this triad of symptoms, including the potentially treatable riboflavin transporter defect.

Ataxia with ocular motor apraxia (AOA) exists in two types: AOA1 is the more common form in childhood and has been described together with ataxia–telangiectasia because of their similarities in Chapter 4 even though its pathophysiology seems closer to that of the spinocerebellar ataxias (see below). One important biological sign is hypoalbuminaemia which is almost always eventually found and is of diagnostic significance but may not be evident for up to 10 years from onset. The disorder is caused by mutations in the aprataxin gene which encodes senataxin, a protein involved in DNA processing and DNA repair. Many progressive conditions can eventually cause this triad of symptoms, including the potentially treatable riboflavin transporter defect.

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AOA type 2 is rarer in some countries (e.g. Japan and Portugal but not France) and has a later onset, usually late in the first decade, the teens or in early adulthood. Progressive ataxia is accompanied by abnormal apractic eye movements in up to 50% of cases, as well as nystagmus, dysarthria and a sensorimotor neuropathy. Intellect is usually preserved. AOA2 is caused by mutations in the SETX gene which encodes senataxin, a protein involved in DNA processing and DNA repair. Serum alpha-fetoprotein is invariably elevated but there are no telangiectases. Serum albumin levels are sometimes low.

A rare but interesting condition seen in Saudi Arabia is spinocerebellar ataxia with axonal neuropathy 1 (SCA1). This is also a disorder of DNA repair due to the absence of the enzyme topoisomerase-phosphodiesterase-1 (TDP1) (El-Khamisy et al. 2005).

Autosomal Recessive Ataxia of Charlevoix–Saguenay

This spastic–ataxic syndrome was originally described in Quebec but has since been recognised in other parts of the world including Europe, Japan, Tunisia and Turkey (Vermeer et al. 2008). It is due to a mutation in the sacsin gene on chromosome 13q12 (Engert et al. 2000). Its phenotype features early-onset ataxia often so severe in the lower limbs as to prevent normal walking but relatively mild in the upper limbs. Marked spasticity, which may precede ataxia, involuntary movements, dysarthria, abnormal eye movements and distal muscle wasting due to a neuropathy develop later. A frequent finding is of a striated ocular fundus due to hypermyelinated fibres radiating from the optic disc, sometimes partially embedding the vessels. Dementia is not a feature. Brain MRI showing cerebellar atrophy mainly in the vermis with linear T2 hypointensities in the pons.

**Case report 3** (courtesy Dr C Burke and Dr M Shekeeb, Brisbane)

A 16-year-old boy of English–Irish parentage had had ataxia dating from around 3–4 years of age. He had mild motor delay predating obvious ataxia. This progressed slowly over a decade and by 16 years of age he was in a relatively stable phase with independent ambulation, a slightly wide base to his gait, spasticity in the lower limbs which were weaker than the upper limbs, nystagmus and normal dorsal column function but with a motor and sensory axonal neuropathy involving all four limbs. Successive brain MRI showed slowly progressive antero-superior vermal atrophy. On a review, his scans from 10 years of age showed transverse linear hypointensities in the pons which have been reported in autosomal recessive ataxia of Charlevoix–Saguenay. This initiated investigation for other features of the disorder. Fundus examination showed prominence of the nerve fibres overlying the central retinal vessels. An optical coherence tomogram showed hypertrophy of the retinal nerve fibre layer. On genetic testing, he was found to have two truncating heterozygous mutations in exon 9 of the SACS gene on chromosome 13q12.12.

**Marinesco–SJögren Syndrome and Progressive Encephalopathy with Peripheral Edema, Hypsarrhythmia and Optic Atrophy**

Two other rare autosomal recessive syndromes comprise a very slowly progressive ataxia and can be dealt with together with the SCAs. Even though their pathology and mechanisms are probably different, they share several clinical features.

Marinesco–SJögren syndrome results from mutations of the SIL1 gene, which encodes a nucleotide exchange factor for BiP, a member of the heat-shock protein family 70 (HSP70), involved as a chaperone in the major functions of the endoplasmic reticulum (Senderek et al. 2005; Krieger et al. 2013). There is probable interference in protein folding. It is associated with cerebellar atrophy predominantly involving the vermis, with early onset of slowly progressive ataxia, cataracts, mild intellectual disability and the development of a peculiar myopathy and sometimes hypogonadism. Electron microscopy reveals autophagic vacuoles, membranous whorls and electron-dense double-membrane structures associated with muscle nuclei (Sewry et al. 1988).
Progressive encephalopathy with peripheral Edema, Hyparrhythmia and Optic atrophy syndrome (PEHO), also termed cerebello-optic syndrome, is a recessive disorder reported primarily from Finland (Salonen et al. 1991), although cases have been observed elsewhere. The main features are seizures of early-onset, mild dysmorphism, peripheral oedema and regression from 3 to 5 months of age. Optic atrophy develops towards the end of the first year (Haltia and Somer 1993). Presence of cerebellar atrophy beyond 18 months is a required diagnostic criterion. Degeneration of the cerebellar granular cells is a prominent finding at autopsy but extensive cerebral changes also evolve. The genetic basis is unknown but autosomal recessive inheritance is likely.

**X-linked Spinocerebellar Ataxia**

Only a handful of cases with X-linked transmission are on record, mostly in adult patients (Caramins et al. 2013). In a few families, X-linked cerebellar degeneration had its onset in infancy or in adolescence (Bolshhauser and Schmahmann 2012). Cases with and without brainstem and spinal involvement may occur in the same lineage. The distinction between these rare forms of spinocerebellar ataxias and cerebellar parenchymal ataxias is hardly possible in cases without genetic studies and/or postmortem examination.

**Maternal Inheritance**

Mitochondrial disorders in the young are commonly associated with ataxia. Conditions which are very likely to produce ataxia as a key manifestation include neuropathy, ataxia, and retinitis pigmentosa (NARP), Leigh syndrome, infantile-onset SCA, Kearns-Sayre syndrome and POLG-1 disorders such as sensory ataxic neuropathy, dysarthria and ophthalmoplegia (SANDO) and mitochondrial recessive ataxia syndrome (MIRAS). These disorders are discussed in the Mitochondrial Disorders section in Chapter 9.

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**DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF FRIEDREICH ATAXIA AND OTHER INHERITED ATAXIAS**

**Differential Diagnosis**

The presence of cardiomyopathy in a patient with a chronic progressive ataxia is an important clue to the diagnosis of FRDA. In contrast, the presence of significant cerebellar atrophy on MRI at presentation, significant intellectual disability, or preserved sensory responses on nerve conduction studies makes FRDA less likely (Schulz et al. 2009).

Vitamin E deficiency can mimic many of the clinical features of FRDA and must be excluded early. It may occur in malabsorption syndromes, including AVED (see the Other Autosomal Recessive Cerebellar Ataxias section), cystic fibrosis, abetalipoproteinemia (in which serum cholesterol is consistently very low), Allagile syndrome and other hepatic disorders. MRI tends to be normal in these ‘metabolic ataxias’.

Ataxia–telangiectasia (see Chapter 4 and Chapter 22) usually has an earlier onset. A history of repeated infections and the finding of conjunctival and cutaneous telangiectases are suggestive, although the latter are usually not evident at initial presentation and may take several years to develop. Alpha-fetoprotein is consistently elevated to about ten times the normal level. Ataxia–ocular motor apraxia type I has characteristic eye movement findings (see above or Chapter 22). The Roussy–Levy syndrome was once considered a forme fruste of FRDA but is usually attributable to one of the hereditary demyelinating neuropathies. The axonal degenerative forms of hereditary motor and sensory neuropathy (e. g. HMSN/CMT type 2), which often are accompanied by similar nerve conduction abnormalities, constitute by far the most common area of misdiagnosis. It is important not to misdiagnose them as their prognosis is much more favourable than FRDA. In general, ataxia is more prominent in FRDA and distal weakness more marked in CMT type 2. Giant axonal neuropathy may be confused if the typical hair changes are lacking but usually has a more severe clinical picture. Sural nerve biopsy or DNA studies will allow distinction. Other disorders which may be confused include chronic GM2 gangliosidosis (where macular cherry red spot is not a feature), alpha-L-iduronidase deficiency and mitochondrial disorders, particularly NARP and POLG disorders (see Poliodystrophies section). Other spinocerebellar degenerations which may, at times, be confused with FRDA include autosomal recessive spastic ataxia of Charlevoix–Saguenay and in older patients, spinocerebellar ataxias (SCA) types 4 and 25. Benign familial chorea due to NXX2–1 mutations may present as a 'pure' cerebellar ataxia. After a few years, chorea becomes the dominant clinical feature (McMichael et al. 2013).

Among numerous other confusing ataxic phenotypes, the recently delineated riboflavin transporter deficiency syndrome may present with an ataxic sensory neuropathy often accompanied by deafness and visual impairment. The diagnosis may be supported by abnormalities in urinary acyl-carnitines and confirmed by testing for mutations in the SLC52A gene (Foley et al. 2014).

**Management**

*Drug treatment:* Bidichandani and Delatycki (2014) have summarised the needs of patients with FRDA in detail. Apart from the use of idebenone and certain drugs being trialled specifically for FRDA, many of the recommendations are applicable to the other spinocerebellar ataxias.

Antioxidants including coenzyme Q10, vitamin E, idebenone (a short-chain analogue of coenzyme Q10) and iron chelation therapy (with deferiprone) have been well-studied in numerous trials.

In a study of 70 children with FRDA aged 8–18 years (Lynch et al. 2010), idebenone treatment for 6 months did not significantly alter neurological function. A recent Cochrane evaluation (Kearney et al. 2012) found
Chapter 10 Heredodegenerative Disorders

that no randomised controlled trial using idebenone or any other pharmacological treatment has shown significant benefit on neurological symptoms associated with FRDA. In several studies, idebenone has shown a positive effect on left ventricular heart mass but this has not been consistently demonstrated (Lagedrost et al. 2011).

Trials of resveratrol, erythropoietin and histone deacetylase inhibitors (modifiers of frataxin expression) are currently in progress.

**Equipment often required and treatment of clinical manifestations**: Prostheses, walking aids and wheelchairs for mobility; speech, occupational, and physical therapy; pharmacological agents for spasticity when present (such as botulinum toxin injections and other systemic agents); orthopaedic interventions for scoliosis and foot deformities; hearing devices for auditory involvement; dietary modifications and placement of a gastrostomy for dysphagia; antiarrhythmic agents, medications for cardiac failure, anticoagulants and pacemaker insertion for cardiac disease; dietary modification, oral hypoglycaemic agents or insulin for diabetes mellitus; antispasmodics for bladder dysfunction; psychological support, both pharmacologic and counselling.

**Prevention of secondary complications**: Exercise and physical therapy programmes to maintain flexibility, optimise physical condition, and prevent contractures; maintenance of healthy body mass index; establishment of appropriate home and work environment to maximise independence and safety; management of dysphagia to prevent aspiration pneumonia.

**Surveillance in FRDA**: At least annual assessment of overall status; examination for complications including spasticity, scoliosis, and foot deformity; annual ECG, echocardiogram, and fasting blood sugar to monitor for diabetes mellitus; hearing assessment every 2–3 years; a low threshold for sleep studies to investigate for obstructive sleep apnea.

**HEREDITARY SPASTIC PARAPLEGIA**

The familial or hereditary spastic paraplegias (HSPs or SPGs) form a heterogeneous group of diseases clinically characterised by spasticity and weakness with exaggerated reflexes predominating in, or limited to, the lower limbs. An SPG is classified as pure if neurological signs are limited to the lower limbs (although urinary urgency and mild impairment of vibration perception in the distal lower extremities may occur). Complicated forms display additional neurological and MRI abnormalities such as ataxia, more significant peripheral neuropathy, intellectual disability, other movement disorders or a thin corpus callosum. However, both clinical types can occur within the same group (dominant) and may be impossible to distinguish from one another and from some of the spinocerebellar degenerations on clinical grounds (Fink and Hereda 1999). Some forms of SPG, especially early-onset forms, are hardly, if at all, progressive: others are really degenerative disorders with more or less rapid deterioration.

Pathologically, the disorders affect predominantly the distal part of axons of the pyramidal tracts and of the posterior funiculi, but may also, in certain forms, involve other neural structures including anterior horn cells.

The group is also genetically extremely heterogeneous: dominant inheritance is most common (Fink 2002), but spastic paraplegias with autosomal recessive inheritance and with sex-linked transmission are also known. Table 10.9 lists the numerous types and their chromosomal location, also indicating the responsible genes and mutant proteins when known.

At least 86 types of SPG are currently known and new types are still being added; 43 responsible genes have been identified (Fink 2014). Autosomal dominant transmission is observed in 70–80% of all cases and typically results in pure HSP. Overall, the commonest form in Western Europe is SPG4. SPG3 is also common (Dürr et al. 2004) especially in childhood, as it rarely commences after the second decade.

In a large combined adult and paediatric series from the Netherlands, symptom onset prior to 18 years was found in 72 of 175 (41%) patients; 47 of the 72 early-onset cases (65%) were autosomal dominant, 12 of 72 (17%) autosomal recessive and 13 of 72 (18%) were sporadic. In children, gait difficulties were the presenting symptom in 81%, at a mean age of 8 years. A complicated phenotype was present in 25% (de Bot et al. 2010).

For autosomal dominant forms, several products of SPG genes are known: ATL1 encoding atlastin (a dynamin-like GTPase) in SPG3A; SPAST encoding spastin (which is involved in microtubule activity subserving axonal transport) in SPG4; NIPA1 (encoding a magnesium transporter) in SPG6 which usually presents in the second and third decades or later; KIF5A in SPG10 and SPG12. REEP1 mutations cause SPG31, another pure form of HSP which has its onset before 20 years in over two-thirds of cases. REEP1 encodes the mitochondrial protein receptor expression-enhancing protein 1.

Autosomal recessive forms include SPG7, due to paraplegin mutations and SPG20 caused by spartin mutations.

The X-linked types include (a) SPG1 due to mutations in the L1 gene encoding LICAM and (b) SPG2 due to PLP1 mutations alleleic to those of Pelizaeus–Merzbacher disease. SPG2 mutations are also responsible for the MASA syndrome (mental retardation, aphasia, spastic paraplegia and adducted thumbs) (see X-linked Paraplegias section and Chapter 7).

The particular clinical and MRI features of these conditions in childhood are well-described by de Bot et al. (2010).

**PURE SPASTIC PARAPLEGINIA (STRÜMPPELL–LORRAIN TYPE)**

Pure spastic paraplegia is characterised pathologically by degeneration of the pyramidal tracts and of the posterior columns below the cervical level and clinically by bilateral paraplegia or paresis with spasticity and increased tendon reflexes.
beginning and predominating in the lower limbs. Involvement of the upper limbs is unusual, but deep tendon reflexes in the arms are often exaggerated (Polo et al. 1993). Bladder disturbances occur in 20% of cases but are often late. Sensory disturbances are mild, affecting only vibration but not position sense.

Pure spastic paraplegia is a fairly common condition: Harding (1981b) in her study of 22 families separated type I cases, with onset below 35 years of age, and type II cases, where the apparent onset occurred after 35 years. She found a dominant inheritance pattern in 19 families and a recessive mode in only three. Considerable heterogeneity has been shown within the ‘pure’ group that can result from mutations at different loci (Kobayashi et al. 1996). Although 40% of Harding’s patients had symptoms by 5 years of age, there is no doubt that mild cases are common and easily go unrecognised. Of the 41 patients in one series, only seven had sought medical advice, and it is a common experience to discover the disease in one apparently healthy parent of affected children, so that actual examination of both parents is essential for diagnosis.

The uncommon recessive forms may have an earlier onset than dominant cases. The children are often slow to walk, clumsy, fall frequently and tend to walk on tiptoes. In rare cases, mild cerebellar symptoms and signs are present. Urinary symptoms are often present, and mild impairment of vibration and position sense may be seen. Motor and sensory nerve conduction velocities are normal. The course of dominant forms is slow and may remain stationary until late in adulthood. Recessive forms may run a faster course.

Occasional cases are seen, however, who present with abrupt deterioration diagnosed as myelitis, and marked fluctuations of signs, in some cases in association with respiratory infections.

COMPLICATED SPASTIC PARAPLEgia

Hereditary spastic paraplegia can occur in association with many different symptoms and signs, thus producing a number of syndromes whose description is often based on only a few cases or even a single family. These syndromes have been mainly described in adults, but onset often occurs in childhood or even infancy. Their inheritance is usually autosomal recessive but dominant cases are known and X-linked inheritance has been recognised (Appleton et al. 1991). They include hereditary spastic paraplegia with ocular and extrapyramidal symptoms, the so-called Ferguson–Critchley syndrome which has finally been shown to be a form of Machado–Joseph disease (SPC3) (Teive et al. 2004); cases of paraplegia associated with dystonia; SPG11 and SPG15; familial spastic paraplegia with amyotrophy, ophthalmia and central retinal degeneration or Kjellin syndrome due respectively to mutations of spatacasin and ZYFVE-zinc finger domain-containing protein 6 (Leys et al. 2000; Hanein et al. 2008); paraplegia and deafness (Wells and Jankovic 1986); paraplegia with palmoplantar keratosis; paraplegia with disordered pigmenta; and paraplegia with isolated intellectual disability (Nicolai et al. 1993).

A complex syndrome featuring optic atrophy, abnormal choreic movements, mild intellectual disability and sometimes ataxia in addition to spastic paraplegia was recognised by Costeff et al. (1989). This has been shown to be associated with 3-methylglutaconic aciduria. A multitude of syndromes can be observed (Fortini et al. 2003) including cases with a sensory neuropathy involving either the small fibres and responsible for trophic lesions or the large fibres without trophic damage (Thomas et al. 1994), with epilepsy, bulbar symptoms (Bertini et al. 1998) and other neurological abnormalities.

The complicated forms often tend to run a faster course than pure paraplegia (Appleton et al. 1991).

SPASTIC PARAPLEgia WITH COGNITIVE IMPAIRMENT AND THIN CORPUS CALLOsum

A characteristic neuroimaging pattern of spastic paraplegia with cognitive impairment and thin corpus callosum (SPG11) (MIM #604260) is a thin corpus callosum in the anterior aspect. White matter signal abnormalities in the corresponding ‘para-callosal’ parts of the frontal white matter are also characteristic (though not specific, as several complicated forms of SPG have white matter abnormalities).

SILVER SYNDROME

The allelic autosomal dominant motor neuron diseases, Silver syndrome/spastic paraplegia 17 (SPG17), distal hereditary motor neuropathy type V and Charcot–Marie–Tooth disease type 2 (CMT2) with predominant hand involvement have been described in association with KIF5A (Goizet et al. 2009), spastin and atlastin mutations but are also caused by gain-of-toxic-function mutations in the BSCL2 (seipin) gene. Detailed phenotypic analyses have revealed that upper motor neurons, lower motor neurons and peripheral motor axons are variously affected in patients with these mutations even in the one family. Ito et al. (2011) showed that the N88S and S90L mutations disrupt the N-glycosylation motif of seipin, enhance ubiquitination, and appear to lead to the production of proteins that are improperly folded, leading to accumulation of the mutant protein in the endoplasmic reticulum.

A similar clinical picture is seen in SPG43 due to C19orf12 mutations (Meilleur et al. 2010).

TROYER SYNDROME

Troyer syndrome (SPG 20) is a rare disease outside the old Amish community in the United States and caused by
mutations of the *spartin* gene which is involved in regulating microtubule stability and synaptic growth. The disorder is characterised by recessive inheritance, slowly progressive course, distal amyotrophy, mild developmental delay and subtle bone anomalies (Patel et al. 2004). The clinical features are similar to the autosomal dominant Silver syndrome (SPG17) (see Silver Syndrome section) due to mutations of the *BSCL2* and other genes.

**BEHR SYNDROME (COMPLICATED OPTIC ATROPHY)**

Behr syndrome is characterised by early optic atrophy associated with pes cavus, ataxia and spasticity with a slow progression (Marzan and Barron 1994, Pizzato and Castroviejo 2001). A neuropathy may be present. Tremor may also be associated (Schramm et al. 2005). Occasional cases with pseudodominant inheritance are on record (Thomas et al. 1984). Recent evidence has implicated *OPA1* mutations in causation (Yu-Wai-Man et al. 2010). This disorder may also be simulated by 3-methylglutaconic aciduria (Costeff et al. 1989).

SPG7 due to *paraplegin* mutations has much in common with Behr syndrome. Its features are dysarthria, dysphagia, optic disc pallor, axonal neuropathy and evidence of vascular lesions, with cerebellar atrophy or cerebral atrophy on cranial MRI.

**X-LINKED PARAPLEGIAS**

X-linked paraplegia type 1 (SPG1) is due to mutations in the *L1CAM* gene of X-linked hydrocephalus and allelic to the MASA syndrome of intellectual disability, adducted thumbs, shuffling gait, and aphasia.

X-linked paraplegia type 2 (SPG2) is a mild form of Pelizaeus–Merzbacher disease due to mutations involving the proteolipid protein (*PLP1*) gene. All transitional forms short of the full-fledged Pelizaeus–Merzbacher leukodystrophy can be observed, and cases of both conditions can occur in the same pedigree. MRI demonstrates a moderate deficiency of myelin in the temporo-occipital lobe. Most patients have a complicated form of spastic paraplegia (Cambi et al. 1996). Affected boys may have mild symptoms of CNS involvement.

Spastic paraplegia type 16 (SPG16) is also an X-linked condition associated with aphasia, reduced vision, nystagmus and mild intellectual disability. The genetic basis is unknown.

In the absence of a compatible family history and negative examination of both biological parents, treatable conditions such as spinal compression, lesions of the parasagittal motor strip and hydrocephalus should be ruled out. To exclude a tumour or syrinx, all index cases require MRI of the brain and spinal cord.

AIDS and HTLV-1 virus infection may produce a very similar syndrome. The latter disorder has been reported in three members of a family indicating the possibility of vertical transmission (Salazar-Grueso et al. 1990). Vitamin B12 deficiency, metabolic conditions such as adrenomyeloneuropathy, other leukodystrophies, glycine encephalopathy, cerebral folate deficiency, homocarnosinosis and hyperargininaemia (Brockstedt et al. 1990) and others should be thought of in priority. Purine nucleoside phosphorylase deficiency may closely resemble spastic paraplegia but is to be suspected in the presence of frequent infections, lymphopenia, anaemia, failure to thrive and low serum uric acid levels. Neurological symptoms may divert the focus of investigations and delay the diagnosis in some cases (Tabarki et al. 2003).

In a child presenting as a typical pure HSP with a family history suggesting autosomal dominant inheritance, mutation analysis of *ATL1* (*SPG3A*) and *SPAST* (*SPG4*) is recommended as the first test of choice. If negative, *REEP1* (*SPG31*) would be the next choice. In suggestive sporadic presentations, where screening tests for other causes of paraparesis are negative, *ATL1* and *SPAST* mutation analysis should be considered (de Bot et al. 2010). Spastic paraparesis without ataxia may rarely be seen in FRDA cases with smaller expanded alleles on the *FXN* gene (Berciano et al. 2002).

**MANAGEMENT OF SPASTIC PARAPLEGIAS**

Treatment is mainly based on physiotherapy and occupational therapy. Walking aids and ankle-foot orthoses are often helpful. When the precise diagnosis of a spastic syndrome remains uncertain, a trial of levodopa should be strongly considered since dopa-responsive syndromes, notably Segawa disease, can present as a typical spastic paraplegia, even without diurnal fluctuation. Genetic counselling and support are crucial.

Botulinum toxin and other anti-spasticity agents such as baclofen, tizanidine, dantrolene as well as drugs to reduce urinary urgency (e.g. oxybutynin) may be useful. Orthopaedic supervision with appropriate intervention for contractures and spinal complications is important.

**CEREBELLAR HYPOPLASIA**

**GENERAL REMARKS**

Cerebellar hypoplasia is a purely descriptive term. It refers to a cerebellum with a reduced volume, but a normal shape. It is a common but nonspecific neuroimaging finding. It can be associated with a highly heterogeneous group of disorders.
Aetiologies include primary (mainly genetic) as well as (pre- and perinatally) acquired conditions. The distinction between primary and secondary causes is important in guiding the diagnostic work-up, prognostication and genetic counselling.

**Table 10.11 Differential diagnosis of cerebellar hypoplasia**

<table>
<thead>
<tr>
<th>Neuroimaging pattern</th>
<th>Group of diseases</th>
<th>Diseases/anomalies</th>
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<tr>
<td>Prenatal infections</td>
<td>Congenital cytomegalovirus infection</td>
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<tr>
<td>Prenatal teratogens</td>
<td>Antiepileptic drugs (phenytoin, valproic acid); retinoic acid; alcohol; cocaine</td>
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<tr>
<td>Chromosomal anomalies</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>NPCA</td>
<td>PCH as defined by Barth</td>
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</tr>
<tr>
<td>Cortical malformations</td>
<td>Lissencephaly (RELN, VLDRL, tubulin genes &gt;&gt; LIS1, DCX, ARX); polymicrogyria (tubulin genes, GPR56); periventricular nodular heterotopia (FLNA); primary microcephaly</td>
<td></td>
</tr>
<tr>
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<td>α-dystroglycanopathies</td>
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</table>

Adapted from Poretti et al. (2014); NPCA, non-progressive cerebellar ataxia.

Imaging patterns of cerebellar hypoplasia

Cerebellar involvement is heterogeneous. From a pattern recognition point of view, cerebellar hypoplasia can be grouped into those with:

- unilateral cerebellar involvement, as ‘unilateral cerebellar hypoplasia’, considered disruptive in aetiology; and PHACE[S] syndrome;
- mainly midline (vermis) involvement: (typical examples: Dandy-Walker malformation, Joubert syndrome, rhombencephalosynapsis – see Chapter 3);
- global cerebellar hypoplasia, affecting vermis and hemispheres.

A subgroup of patients with non-progressive congenital ataxia is found to have dilated interfolial spaces, mimicking cerebellar atrophy. However, since the clinical course as well as the imaging findings are non-progressive, this is considered as a form of ‘hypoplasia’. Therefore, a single imaging study may not definitely allow distinction between hypoplasia and atrophy. The volume reduction in this form of hypoplasia is likely related to a markedly reduced number of granular cells. About 70% of the volume of the cerebellar folia consists of granular cells. The patho-mechanism is not clear (possibly decreased proliferation of granule neuron progenitors).

Clinical spectrum associated with cerebellar hypoplasia

The clinical phenotype associated with cerebellar hypoplasia is wide and depends also on associated brain malformations or additional unrelated symptoms. Generally, children present with muscular hypotonia and global developmental delay and develop cerebellar signs later (Bolduc and Limpopoulos 2009). Neurological findings include truncal...
ataxia (49–93%), hypotonia (47–49%), ocular movement disorders (40–46%), dysarthria (38%), intention tremor (9–35%) and microcephaly (20%) (Wassmer et al. 2003). Seizures are more prevalent than in the general population (28–56%).

Intellectual disability is present in more than 60% of patients and is severe in 35% of them (Wassmer et al. 2003). Speech and language disorders are common and range from mild impairment to total absence of language development. Behavioural abnormalities are also common and 5–20% of patients have autistic features (Wassmer et al. 2003). The spectrum of cognitive and behavioural abnormalities matches the cerebellar cognitive affective syndrome (Schmahmann and Sherman 1998). This syndrome delineates the contribution of the cerebellum to non-motor functions and includes disturbance of executive function, visuospatial disorganisation and impaired visuospatial memory, personality changes and language difficulties.

Aetiological considerations in global cerebellar hypoplasia and pontocerebellar hypoplasia

Table 10.11 summarises the broad spectrum of possible aetiologies (congenital infections, teratogens, chromosomal abnormalities, metabolic disorders, genetic syndromes, non-progressive cerebellar ataxias). For most conditions imaging abnormalities are not specific, and diagnostic work-up has to consider all available information from family history, personal history, clinical findings including extraneural anomalies, and so on. In clinical practice a large proportion of cerebellar hypoplasias remain unexplained.

Non-progressive cerebellar ataxias

The term non-progressive cerebellar ataxia (NPCA) refers to children with early evidence of cerebellar ataxia without progression on follow-up (Poretti and Boltshauser 2012). Ataxia, which is first manifested between 2 and 3 years of age is preceded by hypotonia and delayed motor and language milestones (Steinlin et al. 1998). Cognitive impairment is common and is the most limiting factor in older children and young adults (Steinlin et al. 1999). In NPCA, familial recurrence has been observed repeatedly, mostly compatible with recessive inheritance. In recent years, genetic mutations have been detected in a small fraction of patients. Neuroimaging in NPCA is variable, it can be normal, but often interfolial spaces are dilated, ‘mimicking’ cerebellar atrophy. Some disorders represent ‘pure’ NPCA, while others manifest ‘plus’ symptoms, such as severe epilepsy, hearing impairment and optic atrophy. Some of these patients have been diagnosed as ‘ataxic cerebral palsy’, a potentially misleading term suggesting a residual disorder with low recurrence risk. Rare pedigrees with dominant or X-linked NPCA are on record (Zanni et al. 2012). It is expected that next generation sequencing will facilitate identification of a large number of involved genes.

Recently a new entity was reported with the clinical findings of congenital ataxia, variable degrees of intellectual disability, ocular motor apraxia, high myopia and a characteristic neuroimaging pattern consisting of marked cerebellar dysplasia, cerebellar cysts, abnormal shape of the fourth ventricle, while supratentorial imaging was normal (Poretti et al. 2014). Aldinger et al. (2014) confirmed the phenotype, identified mutations in LAMA1 and suggested it be designated the Poretti–Boltshauser syndrome (MIM #615960).

Pontocerebellar hypoplasia

The use of the term pontocerebellar hypoplasia (PCH) is not uniform. It is often used in a nonspecific descriptive manner to imply volume reduction of pons and cerebellum. In a more restrictive sense, PCH is used for an enlarging clinically and genetically heterogeneous group of autosomal recessively inherited neurodevelopmental disorders. The concept of prenatal-onset degenerative disorders was initially put forward by Peter Barth (Barth 1993). The initial classification suggested two subtypes PCH1 and PCH2, depending on the presence or absence of anterior horn cell degeneration. As of 2014, MIM lists ten types of PCH, some only observed in very few patients/families. PCH3 and PCH8 seem to have a non-progressive course, in contrast to the other types. With increasing experience milder presentations and variants have been described. It is expected that additional genetic forms will be reported. For a current overview, we refer to Rudnik-Schöneborn et al. (2014).

PCH type 1

Clinical features of the initially reported ‘classic’ PCH1 include prenatal onset, congenital respiratory and feeding difficulties, contractures and short lifespan. Subsequent experience pointed to a more prevalent ‘milder’ form with severe hypotonia, generalised weakness and mostly absent motor and speech development. Seizures are not a feature of PCH1 (in contrast to PCH2). Mutations in VRK1 and EXOSC3 have been associated with PCH1. Neuroimaging does not allow distinction of PCH1 from PCH2. There is an imaging spectrum ranging from early and severe volume reduction of pons and cerebellum to later onset and milder evolution. In the severe forms, there is relative sparing of the vermis compared to the hemispheres, giving a ‘drag-only’ pattern on coronal views. In advanced stages, some supra-tentorial atrophy with subsequent ventricular dilatation is common.
PCH TYPE 2

This is the most prevalent PCH form. Typical features include restlessness in the neonatal period, persistent poor sucking and swallowing, secondary microcephaly and marked extrapyramidal dyskinesia. Seizures are prevalent. Developmental progress is usually lacking. Survival is variable. Currently, four subtypes are known based on various gene mutations (TSEN54, TSEN2, TSEN34, SEPSEC3). TSEN54 mutations are by far the most prevalent (>80%). PCH2, PCH4 and PCH5 represent a spectrum of clinical manifestations caused by different mutations in the TSEN genes. TSEN, SEPSEC3 and RARS2 (mutated in PCH6) genes have functions in a common pathway of RNA processing.

DIFFERENTIAL DIAGNOSIS IN PONTOCEREBELLAR HYPOPLASIAS

Cerebellar disruption in preterm infants can mimic the imaging pattern of PCH (Messerschmidt et al. 2005). Distinction from the genetic PCH forms should not be problematic in the whole clinical context. Risk factors for the cerebellar injury are ‘extreme’ preterm birth (<30 weeks gestation), intraventricular haemorrhage, and neonatal complications. Congenital disorders of glycosylation (mostly CDG1a) and some forms of congenital muscular dystrophies (alpha-dystroglycanopathies) can imitate imaging findings of PCH but again, the whole clinical and imaging context should allow distinction from genetic PCH. Distinction from CASK mutations may not be as straightforward. CASK mutations (X-linked, presumed lethal in males, with exceptions) affect mostly females. Typical features are rapidly evolving microcephaly in the first few months, and seizures are prevalent. Imaging findings show a marked reduction of pontine and cerebellar volume, usually with no dragon-fly pattern. Reduced gyration is not consistent with exceptions) affect mostly females. Typical features are rapidly evolving microcephaly in the first few months, and seizures are prevalent. Imaging findings show a marked reduction of pontine and cerebellar volume, usually with no dragon-fly pattern. Reduced gyration is not consistent (Burglen et al. 2012).

Some patients with mutations in tubulin genes display a small pons and cerebellum, but there are usually additional imaging findings (such as callosal dysgenesis, dysmorphic basal ganglia and cortical malformations).

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Infectious Diseases

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Infections of the central nervous system (CNS) remain common life-threatening conditions. Despite recent advances in health care, and the development of new antibacterial and antiviral agents, they still are associated with an unacceptably high mortality and morbidity. Over the past few decades, many different therapeutic agents have been trialled, but few have resulted in any significant improvements in outcome. In the same period, conjugate vaccines have brought about dramatic changes in the epidemiology of bacterial CNS infection; however, there remains a wide range of infectious organisms for which no preventive vaccines exist. Early diagnosis and institution of treatment, careful monitoring of its efficacy and rapid detection of emerging complications give the best chances of an optimal outcome; but until we gain a greater understanding of the pathogenesis and pathophysiology of acute CNS infections, outcomes are unlikely to improve significantly.

BACTERIAL INFECTIONS OF THE NERVOUS SYSTEM

ACUTE BACTERIAL MENINGITIS IN INFANTS AND CHILDREN

Meningitis makes a major contribution to morbidity and mortality worldwide, contributing over 30 million disability-adjusted life-years across all ages according to 2012 estimates [World Health Organization (WHO) 2012c] and is one of the top 20 causes of years of life lost (WHO 2014). Approximately 180 000 children under 5 years of age die annually from meningitis while 393 000 neonatal deaths occur as a result of sepsis, a substantial proportion of which are attributable to meningitis (Liu et al. 2012). Despite a downward trend in rates of meningitis, it remains a leading cause of death especially in resource-poor settings (Liu et al. 2012). Several factors contribute toward this disappointing situation: inadequate access to key vaccinations, delayed diagnosis because of the nonspecific character of the symptoms, emergence of resistant strains of common pathogens, weakness of the immunological defences of the newborn infant, and our inability as yet to prevent the damage caused by the host inflammatory response through adjunctive neuroprotective or anti-inflammatory mechanisms.

EPIDEMIOLOGY OF ACUTE BACTERIAL MENINGITIS

The relative incidence of acute bacterial meningitis varies according to age, socio-economic conditions, geographic location and immunisation policies. In the developed world over the past decade, the epidemiology of acute bacterial meningitis has undergone a dramatic change and the incidence has fallen, whereas in many developing countries it remains high. Vaccination has brought about this radical change by reducing the relative frequency of the three main pathogens: *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*.

*H. influenzae* type B (Hib) used to be the most common form of childhood bacterial meningitis in the UK, with incidence rates ranging from 21 to 44 per 100 000 in those under 5 years of age, a peak age of 6–7 months, and case fatality rates of 2.4–4.3% (reviewed in Heath and McVernon 2002). Hib protein–polysaccharide conjugate vaccine has been introduced into the national schedules of a number of countries worldwide since the early 1990s and has proven to be highly effective at reducing rates of meningitis due to Hib, due to direct effects and herd immunity, in a range of settings. In countries where vaccine coverage is high, Hib meningitis is a rare disease leaving *S. pneumoniae* and *N. meningitidis* as the most common pathogens causing meningitis. However, in many regions of the world where access to the conjugate vaccine is still limited, Hib remains a major cause of CNS infection (Morris et al. 2008).

In 2000, the incidence of pneumococcal meningitis in children under 5 years of age varied from around six per 100 000 in Europe to 38 per 100 000 in Africa, with associated mortality ranging from a case fatality rate of 38% in Europe to 73% in Africa respectively (O’Brien et al. 2009). Long-term neurological sequelae are particularly common following pneumococcal meningitis with rates as high as 38% in some studies. Figures are substantially worse in the developing world (Ramakrishnan et al. 2009; Chandran et al. 2011). There is a seasonal variation, with a peak in the winter months. Younger children are most affected, with 60% of cases occurring in children.
under 2 years of age. A highly effective 7-valent pneumococcal protein–polysaccharide conjugate vaccine (covering seven common disease-causing serotypes) became available in 2000. Since then, 10 and 13-valent pneumococcal conjugate vaccines have been licensed and are being rolled out globally.

Countries that have had pneumococcal conjugate vaccine introduced into their immunisation programmes have seen dramatic reductions in invasive pneumococcal disease, leaving *N. meningitidis* as the most common pathogen causing meningitis. The incidence of invasive disease due to *N. meningitidis* is currently estimated at between 0.11 and 8.9 per 100000 in European countries (Jafri et al. 2013), with overall rates reported as 0.75 per 100000 [European Centre for Disease Prevention and Control (ECDC) 2013] and 0.15 per 100000 in the United States [Centers for Disease Control and Prevention (CDC) 2012b]. Rates can be as high as 230 per 100000 in some regions of Africa, where epidemics commonly occur (Jafri et al. 2013). The most common serotypes are Groups B and C in European countries with serogroup B now dominant (ECDC 2013; Jafri et al. 2013).

Polysaccharide and protein–polysaccharide conjugate vaccines against groups A, C, Y, W135 are available and an outer membrane vesicle vaccine against group B has recently been licensed (although not as yet introduced into many national schedules). Polysaccharide vaccines are mainly used in at-risk individuals and are in the national schedule of only a few countries. Monovalent conjugate vaccines against group A and C are available as well as polyvalent conjugates against A, C, Y, W135. As is the case with the other conjugate vaccines described above, group C conjugate vaccine has proved highly effective in countries where vaccine coverage is high (Ali et al. 2014).

The highest burden of invasive meningococcal disease occurs in sub-Saharan Africa, in an area known as the ‘meningitis belt’, an area that stretches from Senegal in the west to Ethiopia in the east. In the dry season large epidemics with very high incidence rates can occur, mainly due to serogroups A, C and W135 (Jafri et al. 2013; Ali et al. 2014). Current global immunisation campaigns are promoting vaccination in these regions. For example, the Meningitis Vaccine Project has led to the rapid development and roll out of a *N. meningitidis* group A conjugate vaccine in several African countries (Ali et al. 2014) with initial reports of highly successful short-term efficacy (Daugla et al. 2014).

Another worrying epidemiological trend is the emergence of drug-resistant pathogens, with high rates of penicillin, erythromycin and cephalosporin-resistant invasive pneumococcal isolates reported in some European countries. Resistant invasive meningococcal isolates are also starting to emerge (European Centre for Disease Prevention and Control 2011).

**Pathophysiology and Immunology of Acute Bacterial Meningitis**

Effective invasion of the CNS involves four stages: first, adherence and colonisation of the nasopharynx by the pathogen; second, mucosal invasion and subsequent multiplication and bacteremia; third, traversing the blood–brain barrier (BBB) to enter into the subarachnoid space – the exact mechanism of how this occurs is still unclear; and finally multiplication within the subarachnoid space, generating a host inflammatory response.

**Adherence and colonisation**

The exact mechanisms by which bacteria attach to and penetrate the mucosal surface are still unclear. Multiple surface proteins on both the organism and on host cells are involved. In the case of *N. meningitidis*, adhesion is thought to be initially mediated by type IV pili possibly binding to membrane bound CD46 followed by a number of mechanisms to ensure ongoing colonisation, including further surface protein interactions (e.g. adhesins), biofilm production and specialised mechanisms of nutrient acquisition (Trivedi et al. 2011). *S. pneumoniae* uses a number of strategies to initiate and maintain colonisation including expression of molecules which adhere to epithelial cell components (e.g. Chp, CbpA) and bind to extracellular matrix components (e.g. PavA, Eno) and also strategies to disrupt the protective mucus layer and expose host cell surface molecules (e.g. polysaccharide capsule, neuraminidase) (Bogaert et al. 2004; Kadioglu et al. 2008).

**Invasion**

The organism-specific mechanisms by which transition from colonisation to invasion occurs are poorly understood. However, in the case of *S. pneumoniae* it requires a switch in the expression of virulence determinants (including capsular polysaccharide, PspA and CbpA) to allow transport to and survival within an altered microenvironment (Bogaert et al. 2004; Kadioglu et al. 2008). An increasing array of virulence factors which aid adherence and invasion have been identified with different levels of importance at different stages in the process (van der Poll and Opal 2009).

**CNS penetration**

For pathogens to penetrate the CNS, the organism must first survive in the blood stream and then the BBB and/or blood–cerebrospinal fluid (CSF) barrier must be breached. Extracellular bacteria that normally colonise the host’s nasopharynx or digestive tract use various molecular mechanisms to evade host immunity and gain access to the CNS. Some of the mechanisms in which this is achieved by *N. meningitidis* have recently been elucidated. Meningococci interact with host endothelial cells via type IV pili resulting in rearrangement of host cell structure and protein expression and eventual opening of intercellular junctions (Coureuil et al. 2012). Pneumococci take advantage of a similar array of mechanisms to cross the BBB via both intracellular and intercellular pathways (Mook-Kanamori et al. 2011). A variety of mechanisms used by other bacteria commonly causing meningitis have recently been characterised (Kim 2010).
**Multiplication**

Once inside the CSF, an area of impaired host defence, the pathogens are likely initially to survive and multiply. However, their presence stimulates leucocyte migration into the CSF through a multistep process incorporating different adhesion molecules and ligands (e.g. selectins and integrins) with emigration guided by a chemotactic gradient triggered by the presence of the invading pathogen. Leucocytes then destroy the pathogens, and it is this destruction that precipitates the inflammatory cascade that causes the secondary tissue damage (Hoffman and Weber 2009). Activation of the immune response to invading bacteria occurs in part through binding of bacterial components to pattern recognition receptors. For example, Toll-like receptors bind to bacterial cell wall components including lipopolysaccharide from the Gram-negative organisms such as *N. meningitidis* and *H. influenzae* (Ivey et al. 2005), and lipopeptides/peptidoglycans from Gram-positive organisms such as *S. pneumoniae* (Hoffman and Weber 2009), as well as pneumolysins (Mook-Kanamori et al. 2011) and bacterial DNA itself (Deng et al. 2001). After a time-lag of a few hours, pro-inflammatory cytokines and chemokines are induced (Mook-Kanamori et al. 2011; Bociaga-Jasik et al. 2012; Coutinho et al. 2013; Grandgirard et al. 2013; Wall et al. 2014). These precipitate a cascade of other cytokines, chemokines, proteolytic enzymes and reactive oxygen species and nitrogen intermediates from macrophages, neutrophils and platelets.

Vascular congestion and increased vessel permeability result in cytotoxic and vasogenic brain oedema and increased intracranial pressure (ICP), further decreasing cerebral perfusion pressure, increasing the risk of herniation and irreversible brain damage. The CSF volume increases during the first two or three days of disease (Ashwal et al. 1992), along with levels of endotoxin (Mertsola 1991) and of the cytokines mentioned above (Arditi et al. 1989; Mook-Kanamori et al. 2011; Bociaga-Jasik et al. 2012; Coutinho et al. 2013; Grandgirard et al. 2013; Wall et al. 2014). Whether the levels of cytokines are predictive of outcome remains to be determined (Vazquez et al. 2012, Wall et al. 2014).

Ultimately, these pro-inflammatory processes combine to result in endothelial and neuronal injury and dysfunction, resulting in the potential for cerebral oedema and raised intracranial pressure through a number of pathways including vasogenic, cytotoxic and interstitial oedema and increased brain blood volume (Scheld et al. 2002).

**Pathology of acute bacterial meningitis**

The fundamental pathological change is inflammation of the two meningeal coverings of the brain and spine (arachnoid and pia mater) with initial hyperaemia, followed by migration of neutrophils into the subarachnoid space and the production of a purulent exudate. This exudate rapidly increases and extends into the Virchow–Robin spaces and along the penetrating vessels. Within 48–72 hours, inflammatory involvement of these vessels is seen, initially of the subarachnoid arteries and then of the meningeal veins. Such changes can produce thrombosis of involved vessels with haemorrhagic cortical infarction and secondary necrosis. The necrosis may be limited to one vascular territory or diffusely involve a large portion or the whole of the cerebral cortex (Dodge and Swartz 1965).

Oedema (cytotoxic, vasogenic and interstitial) is often present and, in isolation or in association with acute obstructive hydrocephalus due to purulent cisternal exudate, can result in intracranial hypertension and secondary herniation of brain tissue. This in turn can further impede cerebral perfusion (Minns et al. 1989; Scheld et al. 2002), setting the stage for a vicious circle. Apoptotic neuronal damage also occurs. In the case of pneumococcal meningitis this is particularly in the dentate gyrus of the hippocampus. This is of potential importance, as there is evidence that this damage may contribute to meningitis-related learning difficulties (Loeffler et al. 2001). This apoptosis is thought to be a result of host response to various pneumococcal virulence factors, through caspase-dependent and independent pathways (Parthasarathy and Philipp 2012). Organisation of the meningeal exudate may lead to chronic hydrocephalus, especially in young infants. Hydrocephalus can also result from aqueductal stenosis that may supervene as a consequence of ventriculitis. The latter is most common in neonates, being found in as many as 92% of autopsy cases (Berman and Banker 1966).

**Clinical manifestations and diagnosis of acute bacterial meningitis**

The importance of an early diagnosis is self-evident. However, because meningitis is relatively rarely seen in general practice, compared with the frequency of common, mostly viral febrile diseases, late diagnosis remains frequent. Delay in administration of appropriate antibiotics is associated with poorer neurological outcomes (Bargui et al. 2012). Meningitis is often preceded for a few days by fever so that it may be impossible to determine its actual onset. A substantial proportion of patients may have received antibiotics prior to diagnosis (Kaplan et al. 1986), decreasing the likelihood of isolating the infecting organism in culture. Mode of onset can be a prognostic feature: a progressive onset merging with previous disease may predict a more favourable outcome, while a fulminating onset is of ominous significance (Radetský 1992; Kilpi et al. 1993).

Early symptoms and signs of meningitis in both infants and children can be nonspecific contributing to delayed diagnosis. Classic symptoms and signs, including fever, headache, photophobia, neck stiffness, bulging fontanelle and vomiting may not be present, especially in very young children (Amarilyo et al. 2011). A systematic review found that a history from a caregiver of bulging fontanelle or neck stiffness increased the likelihood of meningitis significantly as well as a history of febrile seizures outside the normal age-range for simple febrile convulsions and also reduced feeding. Regarding physical signs, the presence of a bulging fontanelle, clinical neck stiffness, positive Kernig’s or Brudzinski’s sign were predictive of meningitis. High temperature (>40°C) was somewhat predictive; however, it is important to note that the absence of high temperature did not rule out meningitis (Curtis et al. 2010).
A retrospective study of the sequence and timing of symptoms of meningococcal disease in 448 children (including 99 children with meningitis) found a history of preceding symptoms of respiratory tract infection in around a quarter of children. Evolution of symptoms was usually rapid (over 24 hours). In young children, fever was an early feature, whereas in older children headache was earliest. Nonspecific early symptoms of nausea, vomiting and loss of appetite were very common. Subsequent to this, symptoms and signs of sepsis occurred including leg pain, abnormal skin colour and cold hands and feet. These have been highlighted as important early warning signs of possible meningococcal disease that may be of use in primary care settings. More classic signs of meningococcal disease (neck stiffness, bulging fontanelle, photophobia) developed relatively late. Haemorrhagic rash was only seen in 42–70% of cases (Thompson et al. 2006).

Figure 11.1 9-month-old boy in intensive care with extensive purpura fulminans from meningococcal septicaemia.

The presence of a maculopapular rash can be an early sign of meningococcal sepsis, or represent a viral illness. Petechiae or a purpuric rash is suggestive of meningococcal disease (Fig. 11.1), although can also occasionally be found in association with sepsis secondary to Hib, pneumococcus or some viral illnesses (e.g. Echovirus 9). Focal neurological signs such as cranial nerve palsies or hemiparesis usually develop late in the course of bacterial meningitis, or can occur earlier as a complication of raised ICP (particularly VIth nerve palsies). Papilloedema is rarely evident early on; in fact, the presence of papilloedema should raise suspicion of a focal intracranial process such as brain abscess or a mass lesion, and is an indication for neuroimaging prior to lumbar puncture.

As a result of the low frequency of signs that are both specific and sensitive for bacterial meningitis in children (Brouwer et al. 2012), diagnostic investigations are of great importance, although early laboratory test results can also lack sensitivity and specificity. First-line investigations classically include sampling of blood, urine and CSF with or without neuroimaging. An accurate scoring system has been developed and validated which can predict whether a child older than 2 months of age with CSF pleocytosis does not have bacterial meningitis and can possibly be treated safely in an ambulatory setting while awaiting confirmatory culture results. This Bacterial Meningitis Score consists of five predictors (positive CSF Gram stain, CSF neutrophil count ≥1000 cells per mm³, CSF protein ≥80mg/dl, peripheral blood neutrophil count ≥10000 cells per mm³, seizure). If none of these predictors is present then the child is very unlikely to have bacterial meningitis (Nigrovic et al. 2012).

A key step in the diagnosis of bacterial meningitis is lumbar puncture. Concerns as to the possible complications of lumbar puncture can often lead to reluctance by clinicians to perform this procedure, despite its importance in diagnostics and planning of care. The possibility of cerebral herniation brought about as a result of lumbar puncture performed in the context of raised intracranial pressure has been of concern for many years; however, direct evidence for this is lacking (Benjamin et al. 1988; Rennick et al. 1993; Kneen et al. 2002; Brouwer et al. 2012). The theoretical chance of this alongside other rare severe complications of lumbar puncture (uncontrolled haemorrhage, infection) allows a reasonable list of contraindications to lumbar puncture to be constructed (NICE 2010) (Table 11.1).

Older children usually have signs and symptoms classically suggestive of meningitis that will guide clinical decision-making as to whether a lumbar puncture is indicated. Younger children, infants and especially neonates are more likely to

### Table 11.1 Contraindications to lumbar puncture in children suspected of having bacterial meningitis

<table>
<thead>
<tr>
<th>Signs suggestive of raised intracranial pressure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced or fluctuating level of consciousness (GCS&lt;13 or a drop of 2 or more)</td>
</tr>
<tr>
<td>Relative bradycardia or hypertension</td>
</tr>
<tr>
<td>Focal neurological signs</td>
</tr>
<tr>
<td>Abnormal posture or posturing</td>
</tr>
<tr>
<td>Unequal, dilated or poorly responsive pupils</td>
</tr>
<tr>
<td>Papilloedema</td>
</tr>
<tr>
<td>Abnormal ‘doll’s eye’ movement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation abnormalities:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation results outside the normal range</td>
</tr>
<tr>
<td>Platelet count below 100 × 10⁹ per litre</td>
</tr>
<tr>
<td>Receiving anticoagulant therapy</td>
</tr>
<tr>
<td>Local superficial infection at the lumbar puncture site</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
</tr>
</tbody>
</table>

After seizure until vital signs are stabilised and satisfactory

Shock

Extensive or spreading purpura

Adapted from Kneen et al. (2002) and NICE (2010).

GCS, Glasgow Coma Scale.
have nonspecific signs and for this reason a lumbar puncture is recommended as part of the diagnostic workup of all febrile neonates.

The value of computerised tomography (CT) in detecting oedema or increased ICP is extremely limited (Pike et al. 1990; Heyderman et al. 1992; Nickerson et al. 2012), and it cannot predict the risk of coning. CT has been shown to change management in less than 5% of cases, and it delays lumbar puncture on average by 2.5 hours (Gopal et al. 1999). Delaying lumbar puncture for unnecessary CT has been shown to be associated with a decreased yield from CSF culture in adults with meningitis (Michael et al. 2010). In addition, a normal CT does not mean it is safe to perform a lumbar puncture (Nickerson et al. 2012), and in 36% of patients who coned, the CT had been normal. By using stringent patient selection, the use of CT can be dramatically reduced (Hasbun et al. 2001).

Simple febrile convulsions are common in childhood. A recent systematic review and meta-analysis of seizures in the context of fever in children in resource-rich settings found the overall risk of bacterial meningitis to be low (0.2% in those with a simple febrile convolution). The utility of performing routine lumbar puncture in the absence of clinical signs or symptoms suggestive of bacterial meningitis is therefore very low (Najaf-Zadeh et al. 2013). In the context of a classic simple febrile convolution (i.e. in the absence of any symptoms or signs indicative of meningitis) in a child over 12 months a lumbar puncture is not always indicated. If a younger child is unimmunised against Hib, pneumococcus or meningococcus, or if there is concern regarding the possibility of partially treated meningitis (e.g. prior administration of oral antibiotics), then lumbar puncture should be considered (American Academy of Pediatrics [AAP] 2011).

LABORATORY DIAGNOSIS OF ACUTE BACTERIAL MENINGITIS

Cerebrospinal fluid

Examination of the CSF is an essential step. Routine examination of CSF includes: complete cell count, differential leukocyte count, Gram stain, bacterial culture, glucose and protein concentration with nucleic acid amplification tests [e.g. polymerase chain reaction (PCR)] and antigen detection tests in addition when indicated. Characteristically, the CSF is under increased pressure (>18cm H₂O) and cloudy. In some children, however, the fluid may initially be clear and contain only a few cells or be altogether normal with a negative culture but subsequently demonstrate a positive culture when re-examined 48–72 hours later (Teele et al. 1981). Cultures may be positive for pathogenic bacteria in the presence of normal cytological and chemistry findings, if the lumbar puncture is done after bacterial invasion but before the inflammatory response (Onorato et al. 1980). If clinical suspicion persists, repeat lumbar puncture is indicated within 6–12 hours.

Age-related normal CSF parameters have been defined based on historical data (Table 11.2) (Health Protection Agency 2014). Recent studies have called in to question the validity of earlier defined upper limits of normal in young infants and neonates (Martin-Ancel et al. 2006; Kestenbaum et al. 2010; Byington et al. 2011; Srinivasan et al. 2012). It is therefore advised that infants and neonates with values approaching the upper limit of normal who have any symptoms or signs of meningitis should be treated with antibiotics until the diagnosis has been definitively excluded. At times lumbar puncture may result in a ‘traumatic tap’ whereby CSF is contaminated with fresh blood during the procedure. Various methods/formulae have been proposed for calculating whether a white cell count in CSF is significant when this occurs. However, none of these has been validated and caution should be taken when considering a raised white cell count as non-significant in CSF following a traumatic tap (Greenberg et al. 2008; Bonadio 2014; Srinivasan et al. 2012).

Organisms may be seen intracellularly and extracellularly in smears. Gram stain is positive in a substantial proportion of cases of bacterial meningitis, the rate at which this occurs depending on the organism (Brouwer et al. 2010). Counting the number of colony-forming units gives an idea of the concentration of organisms in the CSF. It is possible to isolate an organism and determine its sensitivity to antibiotics in 90% of untreated cases of bacterial meningitis (Bohr et al. 1983). Prior treatment with antibiotics can be associated with lower protein levels and higher glucose in CSF but the white blood cell count does not appear to be affected (Nigrovic et al. 2008). Prior antibiotic exposure can sterilise CSF; the speed at which this occurs depending on the infecting organism (Kanegaye et al. 2001). A raised protein level is usual, both as a result of disruption of the BBB and from local production of immunoglobulins (Maida and Horvatits 1986). The CSF:blood glucose ratio is usually reduced. Blood and CSF glucose levels should therefore be determined simultaneously (Donald et al. 1983). A normal glucose level is found in up to 20% of cases (Lambert 1994) and does not exclude the diagnosis. Patterns of CSF abnormality characteristic of bacterial infection compared to other types of infection (viral, fungal, mycobacterial) have been described:

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**Table 11.2 Normal age-related cerebrospinal fluid values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonates &lt; 6 days</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>0–30 cells × 10⁶ per litre</td>
<td>0–5 cells × 10⁶ per litre</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>Newborn 0–675 cells × 10⁶ per litre</td>
<td>Adults 0–10 cells × 10⁶ per litre</td>
</tr>
<tr>
<td>Protein</td>
<td>Neonates 0.7g/dL</td>
<td>Others 0.2–0.4g/L (&lt;1% serum protein concentration)</td>
</tr>
<tr>
<td>Glucose</td>
<td>&gt;60% of simultaneously determined plasma concentration</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Health Protection Agency (2014).
Table 11.3 Causes of ‘aseptic’ meningitis syndrome

**Infectious causes**

- **Bacteria:** Actinomyces spp., *Borrelia burgdorferi* (Lyme disease), *Brucella melitensis*, Leptospira spp., *Mycoplasma pneumoniae* and *M. hominis*, *Mycobacterium tuberculosis*, atypical mycobacteria, Nocardia spp., *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Treponema pallidum*. Conditions including, for example, bacterial endocarditis, brain abscess and parameningeal suppurations, partially treated meningitis, sinus thrombophlebitis, children with systemic infection
- **Viruses:** Arboviruses (e.g. West Nile virus), tick-borne encephalitis virus, arenaviruses (lymphocytic choriomeningitis), enteroviruses (e.g. polio, coxsackie, echo), parechoviruses, adenoviruses, herpes viruses (e.g. HSV-1/2, HHV-6/7, variella, cytomegalovirus and Epstein–Barr virus), retroviruses (e.g. human immunodeficiency virus), paramyxoviruses (e.g. mumps, measles), orthomyxoviruses (e.g. influenza), parvovirus B19, live viral vaccines
- **Fungi:** Blastomyces dermatitidis, Candida spp., Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Sporothrix schenckii
- **Protozoa:** Amoebae (Naegleria spp.), *Plasmodium falciparum*, *Toxoplasma gondii*, visceral larva migrans
- **Cestodes:** Cysticercosis

**Noninfectious causes**

- Malignancies: Leukaemia, lymphoma, metastatic brain tumours
- **Granulomatous disease:** Sarcoïdosis, Langerhans histiocytosis
- **Collagen and vascular diseases:** Lupus erythematosus, panarteritis, other vasculitides
- **Toxins:** Intrathecal contrast media, air, anaesthetics, systemic toxicity (lead, mercury)
- **Drug-induced meningitis:** (Azathioprine, cytosine-arabinoside, isoniazid, nonsteroidal anti-inflammatory drugs, penicillin, cephalosporins)

**Unknown mechanisms**

Multiple sclerosis, Schilder disease, uveomeningitis syndromes (e.g. Behçet, Harada–Vogt–Koyanagi), Kawasaki disease, Mollaret meningitis

Raised opening pressure, white blood cell count more than 1000 x 10^6 per litre, low glucose, raised protein (Brouwer et al. 2010; Kim 2010; Brouwer et al. 2012). Their significance should not be over-emphasised as results can be variable, especially in the context of early infection and in neonates. Polymorphonuclear cells characteristically predominate although they can also be a feature in viral and mycobacterial meningitis and are not a defining feature. Very high white cell counts with predominantly polymorphonuclear cells are, however, strongly predictive of bacterial meningitis (Spanos et al. 1989).

Positive bacterial culture from CSF is the criterion standard for confirmation of bacterial CNS infection. In the case of prior antibiotic administration, yield from traditional culture methods decreases (Kanegaye et al. 2001; Brouwer et al. 2010). Both sequential-multiplex PCR and 16S ribosomal RNA PCR are quick and useful adjunctive investigations and have good specificity and sensitivity for detecting pathogens in CSF especially in the context of prior antibiotic exposure (Corless et al. 2001; Schuurman et al. 2004; Chiba et al. 2009; Kim 2010; Brouwer et al. 2012; Srinivasan et al. 2012). Latex particle agglutination can be used for the rapid detection of antigens from the three common pathogens and group B streptococci. The sensitivity of this test has been shown in a number of studies to be low and its clinical utility is therefore limited (Brouwer et al. 2010).

In patients with meningitis but no bacteria grown from the CSF or other sites the physician must consider other causes of the aseptic meningitis syndrome. Many aseptic meningitides are due to viral infections, but other causes are possible (Table 11.3). Such children should have a tuberculin skin test (or mantoux) with or without interferon gamma release assay (IGRA) for tuberculosis, and exclusion of other possibly treatable causes. Careful clinical, neuroradiological and laboratory examinations should be considered, as applicable to the individual child.

**Other laboratory procedures**

Blood cultures may be positive in a substantial proportion of cases of bacterial meningitis, the likelihood of this varying according to the infecting organism (Brouwer et al. 2010). Overall blood cultures have been shown to have a sensitivity of 73% and specificity of 88% in children with bacterial meningitis with the probability of isolating the infecting organism highest in neonates (Sarkar et al. 2011). Bacterial PCR performed on blood may also contribute to the detection of causative organism (Carrol et al. 2000; Wu et al. 2008b). Nose and throat cultures are neither sensitive nor specific. Urine cultures and Gram-stained smears of skin lesions may provide clues to the identity of pathogens, the latter immediately (Brouwer et al. 2010). Immuno chromatographic detection of pneumococcal antigen in urine is of use in adults to detect pneumococcal disease (Marcos et al. 2001). However, its utility is limited in children as a result of low specificity resulting from higher rates of asymptomatic pneumococcal carriage leading to a positive test (Charkaluk et al. 2006). Bacteriological study of the middle ear fluid obtained by aspiration in the case of associated otitis media may show the same organism as is present in the CSF and can be used to guide antibiotic therapy.

Alternative diagnostic markers have been assessed including CSF levels of lactate, heparin-binding protein, TREM-1, IL-1β, IL6, IL12, TNFα, complement component B and
complement component 3. Predictive value of serum levels of C-reactive protein (CRP) and procalcitonin have also been addressed in retrospective studies. Some of these markers have good sensitivity and specificity for distinguishing between bacterial and aseptic meningitis. However, small study numbers limit conclusions and the majority of them are not currently in clinical use (Brouwer et al. 2012).

**Neuroimaging of Acute Bacterial Meningitis**

Commonly available imaging modalities of use in CNS infection include cranial ultrasound (in neonates), CT and magnetic resonance imaging (MRI). MRI has benefits over CT in that it is more sensitive, can provide high-resolution imaging and does not involve exposure to ionising radiation. However, scanning can be a lengthy process and may require general anaesthesia (with its associated risks) in order to acquire useful images. Nevertheless, recent advances in availability of different sequences (e.g. diffusion-weighted imaging [DWI], fluid attenuated inversion recovery [FLAIR]) have made this imaging modality invaluable for assessing the effects of infectious processes on soft tissue. Early imaging may be normal, or may show meningeal enhancement with contrast, but its main use is in the exclusion of other CNS pathologies and for the diagnosis of complications such as infarction, abscesses, hydrocephalus, ventriculitis, empyema and venous sinus thrombosis (Klein et al. 1986; Foerster et al. 2007; Nickerson et al. 2012). Patterns of abnormality on imaging may be suggestive of the causative organism; however, there is considerable overlap (Jaremko et al. 2011). In the acute setting, UK National Institute for Health and Care Excellence (NICE) guidelines recommend performing a CT prior to lumbar puncture if there is significantly reduced or fluctuating consciousness or focal neurological signs (NICE 2010). Riordan and colleagues previously suggested the following indications for CT: prolonged depressed consciousness, prolonged partial or late seizures, focal neurological abnormalities, enlarging head circumference, evidence of continuing infection and recurrence of symptoms and signs (Riordan et al. 1993).

**Management of Acute Bacterial Meningitis**

**Antibacterial Chemotherapy**

Antibiotics for meningitis must be able to cross the BBB and be able to kill the infecting organism while resulting in minimal toxicity to the host. Higher than usual doses are sometimes required in order to ensure adequate CSF concentrations although inflammation of the meninges during active infection may enhance CSF drug levels (van de Beek et al. 2012). Frequency of administration should be considered, especially if planning outpatient parenteral antibiotic therapy. Antibiotic decisions should be tailored to the antibiotic sensitivity of an isolated organism. There are three main circumstances when decisions as to which antibiotic to use must be made. The first is when choosing initial empiric therapy, as is usually the case prior to results of laboratory tests being available. The choice of empiric antibiotic will depend on the age of the child (neonate, young infant, older child) and hence the most likely infecting bacteria (Table 11.4) and whether the infection was acquired in the community or in hospital. Local microbiological sensitivity patterns must also be taken in to account. The second circumstance is when a specific bacterium has been isolated and antibiotic cover can be rationalised depending again on local antibiotic sensitivity patterns. The third is when in vitro antibiotic sensitivity of the organism has been formally assessed and can be used to further tailor antibiotic therapy.

With regard to empiric therapy, in children younger than 3 months, Gram-negative organisms (e.g. *Escherichia coli*), group B streptococcus and *Listeria monocytogenes* are more common than in older children and this should guide antibiotic choice. In most regions a combination of third generation cephalosporin and ampicillin or amoxicillin (the latter in view of *Listeria* being resistant to cephalosporins) should provide adequate cover. Despite the almost universal adequacy of this first-line choice, guidelines for first-line antibiotic for neonates with sepsis alone or together with meningitis are highly variable (Fernando et al. 2008; Lutsar et al. 2014). If there is a possibility of resistant Gram-negative organisms (e.g. nosocomial infection) then meropenem may be a better first-line choice. Choice of a third generation

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**Table 11.4** Suggested first-line antibiotic therapy for acute bacterial meningitis (children ≥2 months). Always adjust according to sensitivities, consult local guidelines and consider local patterns of antimicrobial resistance

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Group B streptococcus (S. agalactiae)</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Ampicillin and aminoglycoside</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Meropenem + aminoglycoside</td>
</tr>
<tr>
<td><em>Ceftriaxone</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>Meropenem + aminoglycoside</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Fluclouxillin (high dose) + rifampicin Vancomycin + rifampicin if MRSA</td>
</tr>
<tr>
<td>Pasteurella spp.</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>Meropenem + aminoglycoside</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Chloramphenicol and gentamicin</td>
</tr>
<tr>
<td>Unknown</td>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

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555
ceftriaxone in very young or unwell children (related to exacerbation of jaundice and incompatibility with calcium containing infusions). In children over 3 months, despite the resounding success of conjugate vaccination, haemophilus, meningococcus and pneumococcus are still the most likely organisms causing meningitis. Third generation cephalosporins are usually an adequate first-line choice, cefotaxime being preferred in early stages due to its compatibility with calcium containing infusions. A switch to ceftriaxone can then be made should a prolonged course of antibiotic be required as it has more convenient once a day dosing. In regions where cephalosporin resistance of *S. pneumoniae* is a possibility (or in children travelling from these areas), vancomycin alone or together with rifampicin should be added until formal sensitivities are known.

Once an organism is identified modification of antibiotic choice and treatment duration can be planned. For *S. pneumoniae*, *H. influenzae* and *N. meningitidis*, a third generation cephalosporin is usually adequate although vancomycin alone or together with rifampicin may need to be added if there is cephalosporin resistance. Group B streptococcus may be treated with a third generation cephalosporin or benzylpenicillin or amoxicillin combined with an aminoglycoside. For *L. monocytogenes*, ampicillin/amoxicillin and gentamicin are the preferred option (Klein et al. 1986). Other Gram-negative organisms may be highly resistant, especially when acquired in a healthcare setting. When they are identified in culture a switch to a broader spectrum antibiotic, such as meropenem alone or together with an aminoglycoside, may be considered until formal sensitivities are available. Flucloxacillin is the first-line antibiotic when *Staphylococcus aureus* is the causal organism; however, initial treatment with vancomycin alone or together with rifampicin may be indicated until the organism is confirmed to be non-methycillin resistant staphlococcus aureus (MRSA), especially in regions of high MRSA prevalence (NICE 2010; van de Beek et al. 2012).

Inhibition of growth is not enough, and bacterial concentrations may need to be 10–30 times the minimum inhibitory concentration (Quagliarello and Scheld 1997). This can be achieved, in most cases, with adequate plasma concentration; direct instillation of the drug into the ventricles is only very rarely indicated (Feigin et al. 1992) and a recent Cochrane review of intraventricular antibiotics concluded that this practice should be avoided in neonates as one study found increased relative risk of mortality (Shah et al. 2012). It has been suggested that continuous infusion of antibiotic may be more beneficial in treating meningitis than intermittent bolus dosing. A recent randomised trial set in Africa attempted to assess this by comparing outcomes following cefotaxime infusion vs. cefotaxime bolus dosing in the first 24 hours of meningitis. Results showed no differences between the two strategies for bacterial meningitis overall, but a subgroup analysis suggested that there may be some benefit from continuous infusion for pneumococcal meningitis (Pelkonen et al. 2011). This strategy is not recommended at present.

**Duration of treatment**

Evidence to inform duration of treatment in bacterial meningitis remains limited. Standard duration of therapy for uncomplicated meningitis in children with *N. meningitidis*, *H. influenzae* and *S. pneumoniae* are 7, 10 and 10–14 days respectively (Lin et al. 1985; Jadavji et al. 1986; NICE 2010). A meta-analysis found no difference in outcomes for short versus long course antibiotics in meningitis (without individual analysis by organism) (Karageorgopoulos et al. 2009). A subsequent large randomised controlled trial comparing 5 versus 10 days of intravenous ceftriaxone for bacterial meningitis in children found no difference in assessed outcomes (Molyneux et al. 2011). Nevertheless, national guidance still favours the treatment durations similar to those mentioned above (Tunkel et al. 2004; NICE 2010).

For younger infants and neonates, standard recommended duration of treatment for the commonly infecting organisms *L. monocytogenes* and Gram-negative organisms should be at least 21 days and for group B streptococcus, at least 14 days. These recommendations are again made in the absence of strong randomised controlled trial evidence. In all ages, when the infecting organism has not been identified, duration of empiric therapy should be sufficient to treat the likely organism using the longest recommended treatment course in that age group. If the course of treatment is complicated then longer duration of therapy may be indicated.

**Monitoring of treatment**

‘End of treatment’ lumbar puncture is not recommended in regular cases of childhood meningitis as the cell and chemical composition of the CSF is extremely variable (Schaad et al. 1981; Durack and Spanos 1982). However, any child who remains febrile or does not appear to be responding to treatment, warrants a repeat lumbar puncture, as does meningitis complicating CSF shunt (Chaudhuri et al. 2008).

**Adjuvant and supportive treatment**

Whether to use corticosteroids remains controversial in treatment of acute bacterial meningitis in children (Esposito et al. 2013b), although there is clear evidence of benefit under certain circumstances. A recent Cochrane review found adjunctive steroid therapy to be associated with a reduction in hearing loss in *H. influenzae* meningitis in all settings. It also found a reduction in hearing loss and short-term neurological sequelae in all causes of bacterial meningitis combined in high-income countries. The authors concluded that adjunctive corticosteroids are of benefit in bacterial meningitis in children in high-income countries (Brouwer et al. 2013). The UK NICE guidelines provide additional guidance, recommending that steroids be used in children over 3 months with probable bacterial meningitis indicated by any of: frankly purulent CSF, CSF white cell count more than 1000 cells per µl, raised CSF white cells with protein more than 1mg/dL, bacteria on Gram stain (NICE 2010). A US guideline also recommends their use in this age group (Tunkel et al. 2004). Concerns regarding the contribution of
corticosteroid therapy to an increased risk of delayed cerebral thrombosis in adults with pneumococcal meningitis (Schut et al. 2009) have not so far been raised in paediatric practice.

Ideally, dexamethasone should be given empirically with or before the first dose of antibiotic, continuing a dose of 0.15mg/kg 6-hourly for the first 48–72 hours of antibiotic therapy. The concern raised has been that steroids may delay sterilisation of the CSF; however, in children with cephalosporin-resistant pneumococci, CSF penetration of vancomycin seemed unaffected by adjunctive use of corticosteroids (Morris 2004). A subsequent study in adults has also shown no effect of adjunctive corticosteroids on CSF concentration of vancomycin when treating pneumococcal meningitis (Ricard et al. 2007).

New potential targets for adjuvant therapy are urgently being sought. The use of osmotic therapies to reduce cerebral oedema has been explored. A Cochrane review found no evidence for benefit of glycerol in the treatment of bacterial meningitis in children (Wall et al. 2013), a conclusion supported by the results of a randomised trial of adjunctive glycerol and paracetamol in children with meningitis (predominately pneumococcal) in children in Malawi, which also demonstrated no benefit (Molyneux et al. 2014).

The cascade of cytokines, chemokines, proteases, antioxidants and apoptotic enzymes, among others, that are induced by the host inflammatory response provide many potential targets for neuroprotection. Various models have shown promising results with therapies including inhibition of complement activation, pro-inflammatory cytokines, pattern recognition receptors and caspases as well as modification of leukocyte migration and the use of non-bactericidal antibiotics (reviewed in Mook-Kanamori et al. 2011). The use of a C5-specific antibody in a mouse model of pneumococcal meningitis prevented death in all treated mice, highlighting the future potential of one such novel strategy (Woehrl et al. 2011).

Careful management of fluid and electrolyte balance is essential in meningitis, as both over- and under-hydration may be associated with adverse outcomes. A Cochrane review found insufficient generalisable evidence to guide practice, although there is some evidence that maintenance fluids rather than fluid restriction in the first 48 hours might improve outcomes in settings with high mortality rates and late presentation (Maconochie and Bhaumik 2014). Fluid restriction is not routinely indicated for patients with meningitis, and sufficient amounts of fluids are essential for the prevention of shock. A recent trial of intracranial pressure targeted therapy in adults with bacterial meningitis and low Glasgow Coma Scale (GCS) scores, has shown promising results relating to both morbidity and mortality (Glimaker et al. 2014), whereas a randomised trial in children with CNS infection (the majority of which was bacterial) found cerebral perfusion pressure-targeted therapy to be associated with improved morbidity and mortality when compared with intracranial pressure-targeted therapy (Kumar et al. 2014). The use of these strategies to improve outcomes in the intensive care setting is an exciting and evolving field.

Hyponatraemia frequently represents dehydration, rather than the syndrome of inappropriate antidiuretic hormone (SIADH), and fluid restriction may further compromise cerebral circulation. Arginine–vasopressin concentrations in blood normalise when children with meningitis are given adequate maintenance and replacement fluid therapy, indicating that high levels are a response to dehydration (Powell et al. 1990).

Convulsions should be stopped with intravenous midazolam or lorazepam. If unsuccessful, treatment of status epilepticus should be followed as per local protocols (see Chapter 16). Preventive treatment is used in some centres, although it is not routinely advocated.

Complications of Acute Bacterial Meningitis

Cerebrovascular complications including arterial stroke, venous thrombosis and intracranial haemorrhage are common in the context of bacterial meningitis especially in association with pneumococcal disease (Chang et al. 2003; Kastenbauer and Pfister 2003; Jaremko et al. 2011; Mook-Kanamori et al. 2011; Pryde et al. 2013; Boelman et al. 2014). The aetiology of ischaemic injury has widely been considered to be vasculitic, based on the results of imaging reports and historical histopathological studies. More recently adult post-mortem findings in the context of pneumococcal meningitis have shown that ischaemic damage is not always associated with vasculitis and that intravascular coagulation may also contribute (Vergouwen et al. 2010). The role of endothelial dysfunction and dysregulation of coagulation are currently under investigation (Mook-Kanamori et al. 2011). A recent retrospective case series has highlighted the potential for antithrombotic therapy in prevention of stroke in bacterial meningitis in children (Boelman et al. 2014). The location of ischaemic foci is variable, from localised well-defined areas to diffuse necrotic lesions that may be responsible for multicystic encephalomalacia (Fig. 11.2). Ischaemic lesions can be found in the absence of vascular thrombosis. The inflammatory disruption of small vascular walls within the CNS can permit organisms to invade the parenchyma, producing small foci of septic necrosis. It seems likely that such foci give rise to the cerebral abscesses that in rare cases complicate bacterial meningitis. Spinal cord infarction is an uncommon complication related to vascular involvement (Moffett and Berkowitz 1997; Almasanu et al. 2005). Exceptionally it has been seen as a presenting feature (Boothman et al. 1988). The appearance of bilateral sensory or motor deficit in the course of bacterial meningitis should suggest spinal cord infarction (Glista et al. 1980).

Other unusual neurological abnormalities include movement disorders (Burstein and Breningstall 1986), hypothalamic dysfunction (Karadag-Oncel et al. 2015) and central diabetes insipidus (Greger et al. 1986). Neuroimaging procedures permit a good assessment of the type and location of the responsible lesions. Such lesions may be partly haemorrhagic. Cranial nerve deficits in nontuberculous bacterial meningitis are rare. However, paralysis of the IIIrd, VIth, or less commonly the VIIth cranial nerves can occur as they cross the inflamed leptomeningeal spaces. Opsoclonus has been reported (Rivner et al. 1982).
Seizures are common in children with acute bacterial meningitis, the post-ictal period of decreased consciousness being often longer than that observed following simple febrile convulsion (King et al. 2012). In some cases status epilepticus occurs (Chin et al. 2006) and requires emergency treatment to prevent further long-term damage (see Chapter 16).

Subdural effusion is a recognised complication of acute bacterial meningitis occurring in 20–50% of children with meningitis. The effusions are usually of limited thickness and volume and clinically of little significance (Syrogiannopoulos et al. 1986; Cabral et al. 1987). Most effusions are located over the frontoparietal region bilaterally. The subdural fluid is rarely bloody but has a disproportionately high albumin to globulin ratio (Rabe et al. 1968). Persistent or recurring fever, focal neurological signs and persistently positive CSF cultures are probably more closely related to cortical damage than to the presence of an effusion (Syrogiannopoulos et al. 1986; Snedeker et al. 1990). Large effusions with enlargement of the head or signs of increased ICP are rare but necessitate drainage. Most subdural collections resolve spontaneously. Snedeker and colleagues found that patients with effusion were more likely to have neurological abnormalities and seizures during the acute illness, but that hearing loss, seizures and developmental delay were not more frequent at follow-up (Snedeker et al. 1990). Subdural empyema is rare (Bockova and Rigamonti 2000; Cole et al. 2012). It is often marked by the persistence of fever and infective symptoms and signs in association with focal signs such as convulsions and hemiplegia. The diagnosis is made by neuroimaging that shows
an extra-axial collection with peripheral enhancement (Fig. 11.3). Diffusion-weighted imaging may be helpful in distinguishing a simple reactive effusion from an empyema (Hunter and Morris 2003; Wong et al. 2004; Jaremko et al. 2011).

Raised ICP is common in bacterial meningitis in children (Minns et al. 1989), can be of a severe degree and is a potentially serious complication. It can be due to different mechanisms: hydrocephalus from altered CSF absorption or obstructed flow, or cerebral oedema. Acute hydrocephalus is caused by obstruction to the circulation and resorption of CSF, as a result of the presence of thick leptomeningeal exudate in the basal cisterns or over the cerebral convexity in the vicinity of arachnoid granulations, or consequent to ventriculitis with obstruction of the aqueduct. It is usually transient but can lead to late hydrocephalus if extensive meningeal fibrosis develops. The mechanisms leading to cerebral oedema are most likely multifactorial. They include cytotoxic oedema precipitated by cell damage from the infection, vasogenic oedema due to increased capillary permeability related to the inflammatory response to infection, and interstitial oedema from disturbance to CSF resorption by the normal route. SIADH can occur with acute bacterial meningitis (Patwari et al. 1995) and lead to hyponatraemia and hypotonic extracellular fluid, which can exacerbate the cerebral oedema. However, fluid restriction does not improve outcome and is not currently recommended (Singhi et al. 1995; Maconochie and Bhaumik 2014).

The clinical manifestations of high ICP may not always be obvious. They include a decrease in the level of consciousness, headache and vomiting, tense fontanelle and split sutures, abnormal pupillary response and hypertension with bradycardia (Cushing reflex). Papilloedema is rare, particularly early on. CT may show loss of grey–white differentiation, compression of the ventricles and sulci, and small basal cisterns. MRI may show gyral swelling, and diffusion-weighted imaging can be useful in distinguishing cytotoxic oedema (restricted diffusion) from vasogenic oedema (free diffusion). Monitoring of ICP may be a necessary part of treatment in cases of marked or sustained intracranial hypertension (Goitein et al. 1983; Minns et al. 1989). Treatment consists of raising the head to approximately 30° and administering mannitol or other hyperosmolar agents (to reduce cytotoxic oedema) may help in the acute situation. More aggressive measures are described in Chapter 7. Intracranial hypertension is associated with reduced brain perfusion and reduced cerebral blood flow velocity (McMenamin and Volpe 1984), so even moderate episodes of systemic hypotension can have serious consequences and should be avoided (Kaplan and Fishman 1988). Trials of ICP targeted therapy and cerebral perfusion pressure-targeted therapy show promising results (Glimaker et al. 2014; Kumar et al. 2014).

Ventriculitis is common in neonatal meningitis but is relatively uncommon in older children. When ventriculitis is associated with stenosis of the sylvian aqueduct, infection can become localised (pyocepha lus) and may behave as a cerebral abscess. Ventriculitis can be diagnosed by persistence of positive CSF cultures with or without clinical signs. Neuroimaging may allow identification of ventriculitis, with abnormal enhancement of the ventricular surface and oedema of adjacent periventricular white matter and secondary hydrocephalus. CSF cultures with or without clinical signs. Neuroimaging may allow identification of ventriculitis, with abnormal enhancement of the ventricular surface and oedema of adjacent periventricular white matter (Fig. 11.4). Debris may be present in the ventricular cavities (Fukui et al. 2001). Diffusion-weighted imaging and FLAIR are highly sensitive MRI sequences to detect pus and debris in the ventricles, FLAIR also being of use in detecting ventricular wall abnormalities (Fujikawa et al. 2006). Ventriculitis may respond to adequate doses of parenteral antibiotics, sufficient to allow therapeutic drug levels in the ventricle, but local treatment and drainage may become necessary (Agrawal et al. 2008). If not rapidly treated, hydrocephalus is prone to develop in survivors.

Persistent fever and other septic complications are the result of concurrent bacteraemia. Complications relating to bacteraemia include septic arthritis, pericarditis, pneumonia, endophthalmitis and hypopyon (Kaplan and Fishman 1988). Arthritis appearing after 5–7 days of antibiotic therapy is probably mediated by an immune mechanism and frequently responds to anti-inflammatory agents (Rush et al. 1986). Gastrointestinal haemorrhage, anaemia and disseminated intravascular coagulation can be observed in severe cases, especially but not exclusively with meningococcal meningitis. Fever is prolonged for 10 days or longer in 13% of patients, particularly in pneumococcal disease, and recurs secondarily in
16%. Prolonged fever may be associated with other infectious foci, nosocomial infection or subdural effusion (Lin et al. 1984). Commonly, no cause is found and in such cases, repeat lumbar puncture may be indicated. If the child appears well and CSF values are approaching normal, antimicrobial therapy can generally be discontinued at the usual time.

Neurological Sequelae of Acute Bacterial Meningitis

Long-term sequelae following bacterial meningitis in neonates, infants and children are common and can have lasting socio-economic impact. The most frequently observed sequelae include seizure disorders, hearing/visual impairment, motor deficit, cognitive delay and behavioural problems. These are often found in combination. Several reviews have highlighted that rates of complication vary between studies and according to infecting organism, geographical setting, age at time of infection and duration of follow up (Ramakrishnan et al. 2009; Edmond et al. 2010; Chandran et al. 2011). Edmond et al. summarised results from 132 articles (79% of which included data on children). Overall, the risk of major sequelae was highest for pneumococcal meningitis [24.7% (interquartile range 16.2–35.3%)] compared to meningococcal meningitis [7.2% (interquartile range 4.3–11.2%)] and Hib meningitis [9.5% (interquartile range 7.1–15.3%)]. Risk of major sequelae was approximately three times higher in African and southeast Asian regions compared to European regions. In addition, the risk of major sequelae was significantly higher in those under 5 compared to those over 5 years of age (Edmond et al. 2010). Ramakrishnan et al. reviewed data on children from 37 articles reporting from 21 African countries. Ten post-discharge studies found that 10% of children died following discharge from hospital after bacterial meningitis and that a quarter of survivors had neurological/psychological sequelae (Ramakrishnan et al. 2009). Chandran et al. reviewed 24 papers reporting on 1433 children with data available for long-term follow-up (greater than 5 years following meningitis). The majority of papers were published in North America, Europe and Australia. They found approximately half of the children had one or more long-term sequelae with the majority of these sequelae being behavioural or intellectual disorders, while hearing changes accounted for 6.7% of sequelae and gross neurological deficit accounted for 14.3% (Chandran et al. 2011).

Sensorineural hearing loss of a severe to profound degree has been found to occur in about 10% of children with meningitis (Pomeroy et al. 1990; Taylor et al. 1990; Baraff et al. 1993) and is bilateral in 4–5%. Hearing loss is thought to result from labyrinthitis, presumably due to extension of inflammation from the subarachnoid space through the cochlear aqueduct (Kaplan et al. 1981; Eavey et al. 1985). The risk of deafness is increased if the CSF glucose concentration on admission is less than 1.1mmol/L (Dodge et al. 1984), if seizures occur before admission and if sterilisation of the CSF is delayed. Ceftriaxone treatment is associated with delayed CSF sterilisation compared to ceftriaxone and this may have influenced early dexamethasone trials (Schaad et al. 1990; van de Beek et al. 2007). Deafness appears to set in early in the course of meningitis. However, it is difficult to detect clinically, therefore systematic assessment of hearing should be performed ideally before hospital discharge or within 4 weeks of being fit for testing (Vienny et al. 1984; Cohen et al. 1988; NICE 2010). Repeat examination is recommended after discharge if the results of the initial examination are abnormal. Early evoked responses may be transiently abnormal in approximately 20% of cases, with recovery in one or two months (Vienny et al. 1984). Children with severe or profound deafness should be referred for assessment for cochlear implants as soon as possible (NICE 2010; Bille and Ovesen 2014). The occurrence of deafness is not correlated to the age of the patient or the duration of illness before hospitalisation and is thus unlikely to be prevented by an early diagnosis. The use of dexamethasone treatment decreases the incidence of hearing loss (see Adjuvant and Supportive Treatment section). Ataxia may be of vestibular or cerebellar origin (Kaplan et al. 1981). Virtually all patients are able to compensate for balance deficits in a few weeks or months. A permanent seizure disorder is found in 2–5% of individuals (Pomeroy et al. 1990; Taylor et al. 1990; Baraff et al. 1993) and can be isolated but is often associated with learning difficulties and other neurological sequelae of variable severity.

Chronic hydrocephalus is another potential complication of acute childhood bacterial meningitis (Edmond et al. 2010). It can be either obstructive or communicating and is due to meningeal fibrosis of the basal cisterns or of the brain convexity or to stenosis of the aqueduct of Sylvius by granular ependymitis. Chronic hydrocephalus may follow early obstructive hydrocephalus. More commonly it develops insidiously and may not be recognised for weeks or months. Therefore systematic ultrasound examination of the CNS is indicated following neonatal meningitis, as ventricular dilatation may occur long before any increase in head circumference. Management is by an external drain in early cases, later by insertion of a shunt. Other neurological sequelae include hemiplegia, quadriplegia and limb impairments, and occur in 1–4% of individuals. Blindness following purulent meningitis is rare. It may be due to intraocular pathology, optic neuritis, or be of cortical origin.

PARTICULAR FORMS OF ACUTE BACTERIAL MENINGITIS

Neisseria Meningitidis (Meningococcus)

*N. meningitidis*, a Gram-negative diplococcus, is a relatively common cause of bacterial meningitis in Western countries, occurring predominantly in the winter months (European Centre for Disease Prevention and Control 2011) and with a primary peak incidence in the under-5s and a secondary peak in teenagers (CDC 2012b). Thirteen subtypes or serogroups have been identified, with six having potential to cause...
invasive disease (A, B, C, W, X, Y) (Harrison et al. 2013). Serogroup B, C and Y are the most common causes of invasive disease in Europe and North America (Control 2011; European Centre for Disease Prevention and Cohn et al. 2013). The incubation period is variable. Disease usually manifests in the first week after nasopharyngeal acquisition of a pathological strain, but the incubation period can extend to several weeks (Devine et al. 1970; Edwards et al. 1977; Neal et al. 1999). Risk factors for younger children have been identified as preceding viral respiratory tract infection (Jensen et al. 2004; Jansen et al. 2008), mannose binding lectin deficiency (Hibberd et al. 1999), overcrowding (Moodley et al. 1999), lower socio-economic class and passive smoking (Stanwell-Smith et al. 1994). Risk factors for adolescents include preceding illness, kissing multiple partners, being a university student and preterm birth (Tully et al. 2006).

Nasopharyngeal carriage is a necessary precursor to invasive disease. The organism is carried in the nasopharynx asymptomatically, and it is estimated that around 10% of the population carry N. meningitidis at any given time with a peak in carriage in older adolescence (Cartwright et al. 1987). The two main forms of meningococcal disease are meningococcal septicaemia and meningococcal meningitis, although a combination of both can occur (Thompson et al. 2006). Meningococcal bacteraemia without sepsis has been documented in children, sometimes referred to as ‘occult bacteraemia’ (Sullivan and LaScola 1987). Evolution of meningococcal infection from first symptoms to severe disease can be very rapid, over the course of hours. Early clinical signs of meningococcal disease in children are quite nonspecific and include leg pain, cold peripheries and abnormal skin colour. More classically described features of invasive meningococcal disease such as non-blanching rash, meningism and reduced consciousness occur later in disease course (Thompson et al. 2006). The rash can appear initially as a blanching erythematous rash similar to a viral exanthem; however, it can rapidly progress to become petechial or purpuric (Granier et al. 1998; Thompson et al. 2006), the most dramatic skin manifestation of meningococcal sepsis being purpura fulminans (see Fig. 11.1) (Darmstadt 1998). Bacteria can be identified from Gram staining of needle aspirates of skin lesions (Periappuram et al. 1995). Shock can be very severe requiring substantial fluid resuscitation and inotropic support. This can be exacerbated by adrenal insufficiency as a result of bilateral adrenal haemorrhage in fulminant disease (Migeon et al. 1967). Myocardial dysfunction is well documented and is in part brought about by negatively inotropic factors in serum such as IL6 (Pathan et al. 2004). Focal meningococcal infection of other sites including joints, eyes and heart may occur but are rare. Complications resulting from immune complex mediated disease are more common and can include arthritis, episceralitis, pericarditis and vasculitis (Goedvolk et al. 2003).

Treatment is with antibiotics, usually a third generation cephalosporin as resistance rates are still relatively low, and supportive care including careful management of shock, myocardial insufficiency and raised intracranial pressure if present. In the United States, overall mortality from meningococcal meningitis is currently estimated at 5–18% while that of meningococcal sepsis is 5–20% (CDC 2012b). Deficiency in the terminal complement pathway, properdin or IgG2 or 4 may predispose to invasive or recurrent meningococcal disease (Bass et al. 1983; Davis et al. 1983; Ross and Densen 1984; Nielsen et al. 1990) but screening for these in the absence of a preceding history of recurrent infection is unlikely to demonstrate an underlying immunodeficiency (Hoare et al. 2002). Meningitis associated with such complement deficiency is often mild and due to uncommon serogroups (Fijen et al. 1989). Host and microbial factors associated with a more severe disease course have recently been identified including meningococcal factor H binding protein variants (Piet et al. 2012) as well as variants of human complement factor H (Davila et al. 2010). Adjunctive treatment with activated protein C showed initial promise in the treatment of severe meningococcal disease. However, its use is currently not recommended as trials in children have failed to demonstrate efficacy (Nadel et al. 2007; NICE 2010).

The risk of developing the disease for household contacts is about 1000 times the endemic attack rate. Antibiotic prophylaxis is therefore recommended for household, day-care centre and nursery school contacts of a patient with meningococcal meningitis. Local guidance as to which antibiotic to use and duration of prophylaxis should be followed. Vaccines for most serotypes are now available (see Epidemiology section).

**Streptococcus Pneumoniae (Pneumococcus)**

*S. pneumoniae*, a Gram-positive paired diplococcus, is one of the most common causes of invasive bacterial disease in children worldwide. In 2000 there were an estimated 103,000 cases of pneumococcal meningitis in children under 5 years of age globally with an overall case fatality rate of 59%. The case fatality rate varied from region to region with an estimate of 73% in Africa and 38% in Europe (O’Brien et al. 2009). Invasive pneumococcal disease is more common in winter months, in temperate climates, and has a bimodal age distribution, being found mainly in the very young and the elderly (European Centre for Disease Prevention and Control 2011). There are currently over 90 serotypes known, but most disease is caused by only a few serotypes with serotype frequency varying by clinical syndrome (Hausdorff et al. 2000) and geographical region (McIntosh and Reinert 2011; Weinberger et al. 2011). The pattern of serotypes causing invasive pneumococcal disease has been changing over the last decade as a result of the introduction of first 7-valent pneumococcal conjugate vaccine (covering seven serotypes) and then 13-valent pneumococcal conjugate vaccine (covering 13 serotypes) into the national schedules worldwide (McIntosh and Reinert 2011; Navarro Tórne et al. 2014). The 13-valent pneumococcal conjugate vaccine covers 80–90% of invasive serotypes in developed countries, less in the developing world (McIntosh and Reinert 2011). The 23-valent pneumococcal polysaccharide vaccine covers even more serotypes. However, it has
suboptimal immunogenicity and efficacy in young children (Borrow et al. 2012).

Medical risk factors for invasive pneumococcal disease (and indications for additional pneumococcal vaccination) include CSF leak, cochlear implant, sickle cell disease, congenital or acquired asplenia or splenic dysfunction, human immunodeficiency virus (HIV) infection, nephrotic syndrome, some immunosuppressive chemotherapeutic agents and primary immunodeficiency (CDC 2010). Recently described rare autosomal recessive conditions resulting in deficiency of myeloid differentiation factor 88 (MyD88) and interleukin-1 receptor-associated kinase 4 (IRAK-4) have been shown to be particularly associated with severe recurrent invasive pneumococcal disease (including meningitis). These molecules are both involved in innate immune responses to bacterial pathogens (Picard et al. 2010).

Pneumococcal nasopharyngeal carriage is common in young children (Hendley et al. 1975) and is a prerequisite for invasive disease (Simell et al. 2012). Pneumococcal meningitis has a relatively high case fatality rate (European Centre for Disease Prevention and Control 2011) and more frequent/severe sequelae (Edmond et al. 2010) compared to other causes of meningitis. Hearing loss is more common in pneumococcal meningitis than other bacterial meningitis and this can be associated with ataxia (Koomen et al. 2003). Ischaemic stroke seems to be particularly associated with pneumococcal meningitis (Pryde et al. 2013). Diagnosis is made by either isolating the organism from blood or CSF, or from rapid antigen testing or PCR. A third generation cephalosporin is often adequate to treat pneumococcal meningitis. However, increasing incidence of antibiotic resistance in some regions has led to guidelines recommending addition of vancomycin in areas of high antibiotic resistance or following travel to one of these areas (see Epidemiology section).

**Haemophilus Influenzae Type B**

*H. influenza* is a small Gram-negative pleomorphic coccobacillus. It is either encapsulated or unencapsulated, with encapsulated strains being typeable. Encapsulated strains are classified into six types (a–f) (Musser et al. 1988). Over 90% of invasive disease was caused by type b in the pre-conjugate vaccine era. It is now a rare cause of meningitis and invasive disease in the developed world, thanks to the introduction of the type b conjugate vaccine (European Centre for Disease Prevention and Control 2011). The proportion of meningitis in children caused by non-type b encapsulated *H. influenzae* and non-encapsulated *H. influenzae* has subsequently increased in settings where vaccine has been introduced in to national schedules (Ladhani et al. 2010; Ulanova and Tsang 2014; Van Eldere et al. 2014), but Hib is still common in those countries where vaccination is not available. The WHO estimates that in 2008, 203 000 deaths occurred in children under 5 years of age due to invasive Hib infection and that 42 100 of these deaths were due to meningitis (WHO 2012a). Hib meningitis is primarily a disease of infants and young children with approximately 60% of cases in children under 5 years of age occurring before the age of 12 months (WHO 2002).

Diagnosis is confirmed through isolation of the organism or by PCR. An extensive WHO review found the overall mean case fatality rate of Hib meningitis in children to be 13.8%. The mean case fatality rate in developing countries was 17.3%, whereas in industrialised countries it was 3.2% (WHO 2002). Sequelae occur in a substantial proportion of children (see Neurological Sequelae section), with a poorer outcome in more complicated cases. Subdural effusions can often complicate the disease but are of limited clinical significance (Snedeker et al. 1990). Hearing loss is one of the main complications; its incidence can be reduced with steroid therapy (NICE 2010). Treatment is with ceftriaxone or similar third generation cephalosporins as resistance is rarely reported. Prophylactic antibiotics for contacts of cases of invasive Hib disease are recommended as per local guidance.

**Rarer Causes of Purulent Meningitis**

There are many other more rare causes of purulent bacterial meningitis in children, infants and neonates. These frequently occur in the context of risk factors such as neurosurgery with insertion of foreign material (ventriculoperitoneal or ventriculo-atrial shunt) or a congenital anatomical defect involving the CNS or primary/secondary immunodeficiency. *S. aureus* and *Staphylococcus epidermidis* are both possible organisms causing meningitis following neurosurgery. Outside the neonatal period, meningitis due to Gram-negative bacteria is unusual and should prompt investigation for underlying risk factors (Tebruegge and Curtis 2008). Meningitis due to anaerobic bacteria is rare and occurs predominately as a complication of respiratory tract infection e.g. sinusitis or shunt infections (Brook 2002). A list of possible causes of purulent meningitis is provided in Table 11.5, although this is by no means exhaustive. Treatment of meningitis due to these rare pathogens frequently needs to be tailored to the needs of the individual patient but may require prolonged courses of intravenous antibiotics.

**RECURRENT BACTERIAL MENINGITIS**

Recurrent bacterial meningitis in a child should lead to a thorough assessment for an underlying condition leading to susceptibility. Infecting organism, comorbidity and age at onset may provide a clue as to the reason for susceptibility; however, it may not immediately be obvious.

Recurrent bacterial meningitis can occur in children with an underlying dural fistula (congenital or acquired) facilitating infection of the nervous system, but can also occur in the context of congenital or acquired immunodeficiency (Table 11.6). Responsible pathogens include *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *S. aureus*, *E. coli*, *Klebsiella* spp., *Proteus* spp.,
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Salmonella spp. The first three organisms are particularly associated with defects involving communication between the upper respiratory tract and the CNS. Recurrent pneumococcal meningitis can also be associated with a range of primary or secondary immuno-deficiencies. Recurrent meningococcal meningitis has been reported in association with complement deficiency. Gram-negative organisms are associated with lumbosacral defects, whereas Salmonella spp. are particularly associated with HIV infection (Lieb et al. 1996; Tebruegge and Curtis 2008).

A CSF leak occurs in approximately 2% of all head-injured patients. The majority of cases resolve spontaneously. They can persist, however, and cause recurrent meningitis. On occasion recurrent meningitis may be the presenting feature of an occult CSF leak from a past injury (sometimes after a number of years) (Friedman et al. 2000). Pneumococcus is the most commonly reported infecting organism (Lieb et al. 1996; Friedman et al. 2000; Tebruegge and Curtis 2008).

Table 11.5 Rarer causes of purulent bacterial meningitis in children, infants and neonates

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria monocytogenes</td>
<td>Acinetobacter species</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Aeromonas species</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>Bacteroides species</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>Citrobacter species</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>Enterobacter species</td>
</tr>
<tr>
<td>Group A streptococcus (Streptococcus pyogenes)</td>
<td>Fusobacterium species</td>
</tr>
<tr>
<td>Non-anthracis Bacillus species</td>
<td>Klebsiella species</td>
</tr>
<tr>
<td>Propionibacterium species</td>
<td>Pasteurella species</td>
</tr>
<tr>
<td>Actinomyces species</td>
<td>Proteus species</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
<td>Pseudomonas species</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>Salmonella species</td>
</tr>
<tr>
<td></td>
<td>Serratia species</td>
</tr>
<tr>
<td></td>
<td>Veillonella species</td>
</tr>
<tr>
<td></td>
<td>Yersinia pestis</td>
</tr>
<tr>
<td></td>
<td>Burkholderia pseudomallei</td>
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Table 11.6 Causes of recurrent bacterial meningitis in children

<table>
<thead>
<tr>
<th>Anatomical:</th>
<th>Immunodeficiency:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial/cervical defects:</td>
<td>HIV</td>
</tr>
<tr>
<td>Meningocele/meningoencephalocele</td>
<td>Complement deficiency</td>
</tr>
<tr>
<td>Congenital skull defects (ethmoid, petrosal, sphenoid)</td>
<td>Agammaglobulinaemia</td>
</tr>
<tr>
<td>Dermoid cyst/epidermoid cyst/dermal sinus tract</td>
<td>IgG subclass deficiency</td>
</tr>
<tr>
<td>Neurenteric cyst</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>Inner ear abnormality</td>
<td>IRAK-4 deficiency</td>
</tr>
<tr>
<td>Mondini dysplasia</td>
<td>Asplenism (congenital or acquired)</td>
</tr>
<tr>
<td>Head injury/basal skull fracture</td>
<td>Other</td>
</tr>
<tr>
<td>Lumbosacral defects:</td>
<td>Chronic otitis media/mastoiditis</td>
</tr>
<tr>
<td>Meningocele</td>
<td>Adapted from Tebruegge and Curtis (2008).</td>
</tr>
<tr>
<td>Dermal sinus/dermoid cyst</td>
<td></td>
</tr>
</tbody>
</table>

Non-traumatic fistulae (as listed in Table 11.6) may be difficult to detect through clinical examination alone. In the context of recurrent meningitis, detailed examination of the skin, especially the occipital and lumbosacral regions, is required along with thorough otological examination. High-resolution CT or MRI may be required, and ultimately CT or radionuclide cisternography may be required to pinpoint the exact location of a defect relating to recurrent meningitis (Tebruegge and Curtis 2008).

Initially, empiric therapy should be used directed against the most likely infecting organism. Following identification of the organism more directed therapy may be initiated. Prevention of recurrence depends upon the underlying risk factor with surgery being indicated for anatomical defects (Lieb et al. 1996). Antibiotic prophylaxis and vaccination against pneumococcus should be considered.

BACTERIAL MENINGITIS IN NEWBORN INFANTS

The range of organisms causing bacterial meningitis in the first few months of life is different from that for older children and adults. In developed countries, group B streptococcus and E. coli predominate as causative organisms, especially in the
first weeks after birth. Organisms discussed in the Peculiarities of Particular Forms of Acute Bacterial Meningitis section increase in frequency as the child ages.

There are few up-to-date thorough epidemiological investigations of neonatal meningitis. Three studies from the UK, however, have provided a relatively robust picture of neonatal meningitis in the developed world over the past three decades. The first summarised data on meningitis in children under 1 year of age from England and Wales over a 2-year period from 1985 to 1987. The incidence of meningitis was 0.32 per 1000 in the first month (0.22 per 1000 confirmed bacterial) and 1.6 per 1000 births in the first year. Case fatality rate was 19.8% for neonates and 5.4% for post-neonatal infants. Group B streptococcus (28%), E. coli (18%), and Listeria monocytogenes (5%) were the most frequently reported organisms in neonates, whereas H. influenzae (30%), pneumococcus (10%) and meningococcus (30%) were more common after 1 month of age. Meningitis due to group B streptococcus occurred up to 6 months of age and had a 25% mortality (de Louvois et al. 1991).

The second study summarised data from the same region during an 18-month period from 1996 to 1997 for all infants under 1 month of age. The incidence of meningitis was 0.39 per 1000 births (0.21 per 1000 confirmed bacterial). Meningitis was attributable to group B streptococcus in 25% of cases and to E. coli in 10% of cases. Overall case fatality rate was 6.6% (12% for group B streptococcus meningitis, 15% for E. coli). Complications due to ventriculitis, hydrocephalus, relapse or convulsions were reported in 26% of cases (Holt et al. 2001).

The third study summarised data from the UK and Ireland on meningitis in infants less than 90 days old, over a 13-month period from 2010 to 2011. The incidence of bacterial meningitis was 0.38 per 1000 live births (0.27 per 1000 for neonates). In culture confirmed bacterial meningitis in neonates, 58% were due to group B streptococcus, 15% E. coli, 6% S. pneumoniae, 5% L. monocytogenes. Incidence of N. meningitidis and S. pneumoniae increased with age, predominating after 3 months; however, group B streptococcus remained a relatively common pathogen. Overall case fatality rate was 7.6% and was higher for preterm and low birthweight infants and following pneumococcal meningitis (Okike et al. 2014a). All three studies found a higher incidence in infants with low birthweight and those with low gestational age (de Louvois et al. 1991; Holt et al. 2001; Okike et al. 2014a).

Taken together these three studies highlight that the pattern of causative organisms has not significantly changed in neonatal bacterial over the past 30 years in England and Wales. This is despite efforts to prevent group B streptococcus disease in particular through screening and the use of intrapartum antibiotics. Case fatality rates have improved, in particular for group B streptococcus; however, the incidence remains unacceptably high and long-term sequelae are often severe (see below). The finding of group B streptococcus and E. coli being the predominant organisms is in agreement with studies from the United States and elsewhere in Europe (Gaschignard et al. 2011; Thigpen et al. 2011). Other much less frequently isolated organisms in the neonatal period include Gram-negative organisms (Pseudomonas spp., Klebsiella spp., Enterobacter spp., H. influenzae, Citrobacter spp., Serratia spp.) and Gram-positive organisms (coagulase negative staphylococcus, S. aureus, Enterococcus fæcalis, Streptococcus pyogenes, Streptococcus bovisi) (de Louvois et al. 1991; Holt et al. 2001; Polin and Harris 2001; Gaschignard et al. 2011; Thigpen et al. 2011; Okike et al. 2014a). In the developing world, differences in the organisms causing bacterial meningitis in early life compared to older children and adults are also observed. However, the relative predominance of organisms such as group B streptococcus, E. coli, L. monocytogenes and pneumococcus varies according to geographical region. Mortality rates are much higher (40–58%) in these settings (Furyk et al. 2011).

Clinical diagnosis of meningitis in neonates can be challenging as neonates frequently present with nonspecific signs compared to older children and adults. Common presenting symptoms include temperature instability, irritability, poor feeding, seizures, respiratory distress, apnoeas and bulging fontanelle (Pong and Bradley 1999). The majority of these can be the presenting features of bacterial sepsis in general (although they are often seen together). Early-onset neonatal meningitis and sepsis share a number of common risk factors including: invasive group B streptococcus in a previous infant maternal group B streptococcus colonisation or bacteriuria, prelabour rupture of membranes, preterm birth following spontaneous labour, prolonged rupture of membranes in a preterm birth, intrapartum fever or chorioamnionitis, suspected/confirmed infection in another infant in multiple pregnancy (Polin and Harris 2001; NICE 2012). In view of the nonspecific clinical presentation, it is recommended that young infants should be fully assessed for sepsis and meningitis when presenting with these symptoms (including lumbar puncture except in one of the rare circumstances when it is contraindicated) and there should be a low threshold for commencing empiric antibiotic therapy while awaiting test results (especially in the context of existing risk factors for sepsis) (Galiza and Heath 2009; NICE 2012).

As discussed in the Laboratory Diagnosis section, the normal ranges for CSF parameters in the neonatal period differ from those in later infancy and childhood. Furthermore, these normal ranges are again different in the context of prematurity. Attempts have been made to provide reference ranges (Polin and Harris 2001; Srinivasan et al. 2012). However, in view of the potentially severe long-term sequelae, if the clinical picture is suggestive of invasive bacterial infection and the CSF values are approaching the upper limit of ‘normal’, it is prudent to recommend taking a cautious approach and to treat as for confirmed bacterial meningitis, irrespective of isolation of an organism. It is important to note that bacterial cultures can be positive even in the context of CSF findings within published reference ranges (Polin and Harris 2001; Galiza and Heath 2009; Srinivasan et al. 2012). Repeating a lumbar puncture 48–72 hours into antibiotic therapy is
recommended by some, in order to detect persistent culture positivity which may be indicative of antimicrobial resistance or complications such as empyema or abscess, although if there is good clinical recovery and the antibiotic choice is appropriate to the isolated organism this may not be necessary (Pong and Bradley 1999; Polin and Harris 2001; Heath et al. 2003; Galiza and Heath 2009; NICE 2010). Routine repeat lumbar puncture at the end of therapy is not currently recommended in uncomplicated cases (Heath et al. 2003; Tunkel et al. 2004; Galiza and Heath 2009; NICE 2010).

Likely organism, and hence choice of empiric antibiotics, varies with gestational age, birthweight, comorbidity and whether the infection is early or late onset, nosocomial or community-acquired. Choice of first-line empiric therapy for neonatal sepsis varies considerably between centres (Fernando et al. 2008; Lutsar et al. 2014). Ideally it should be guided by local patterns of microbial infection and prevalence of resistant organisms. In most settings, if meningitis is strongly suspected then a combination of third generation cephalosporin plus ampicillin/amoxicillin should provide adequate cover (Tunkel et al. 2004; Hoffman and Weber 2009; Brouwer et al. 2010; NICE 2010; van de Beek et al. 2012). Once an organism is isolated, antibiotic choice can be more targeted. The evidence base on which to base recommendations is small; however, it is generally recommended that group B streptococcus meningitis is treated with amoxicillin/ampicillin or penicillin plus an aminoglycoside or with a third generation cephalosporin for at least 14 days, L. monocytogenes should be treated with amoxicillin/ampicillin for 21 days plus gentamicin for at least the first 7 days and Gram-negative bacterial meningitis requires 21 days of a third generation cephalosporin. Information on in vitro sensitivity of isolated organisms can subsequently guide directed therapy.

If the index for suspicion is high for bacterial meningitis but no organism is isolated, then a 14 day course of a third generation cephalosporin plus amoxicillin/ampicillin should be adequate. Intraventricular antibiotics are not currently recommended (NICE 2010; van de Beek et al. 2012; Shah et al. 2012). No adjunctive therapy has so far been shown to improve outcome. Corticosteroids are not recommended for neonatal meningitis (Galiza and Heath 2009; NICE 2010). There are few recent trials of different treatment strategies in bacterial meningitis in early infancy and the neonatal period (Oeser et al. 2013). A trial is currently underway evaluating the efficacy, safety and pharmacokinetics of meropenem in this context (Neomero 1 and 2: NCT01551394, NCT01554124).

Imaging can be used to assess for complications of neonatal bacterial meningitis. MRI, CT and cranial ultrasound scan all have a role. Potential complications include cerebral oedema, infarction, raised intracranial pressure, hydrocephalus, ventriculitis, empyema and cerebral abscesses, the latter being particular associated with Citrobacter spp., Serratia spp. and Proteus spp. (Polin and Harris 2001; Jaremko et al. 2011; Schneider 2011) (Fig. 11.5). The pattern of abnormality can provide clues as to the likely infecting organism (Jaremko et al. 2011). Electroencephalogram (EEG) can be useful in the assessment of clinical and subclinical seizures and may be of prognostic value (ter Horst et al. 2010).

Outcomes following neonatal meningitis in the developed world are worse than those in older children. In a case series from the UK, the rate of severe disability following neonatal meningitis was around 23% overall and sequelae included cerebral palsy, epilepsy, hearing impairment and developmental delay (de Louvois et al. 2005). A study from the United States reporting outcomes in group B streptococcus meningitis found the incidence of sequelae (seizures,
hypertonicity, dysphagia) to be 22% among survivors (Levent et al. 2010). Outcomes are worse in Gram-negative bacterial meningitis with 61% of survivors having long-term sequelae (seizures, hydrocephalus, physical disability, developmental delay, hearing loss) (Unhanand et al. 1993). Neurodevelopmental outcomes for low weight or preterm infants are worse in those suffering severe bacterial infection including meningitis (Stoll et al. 2004).

Incidence and neurodevelopmental outcomes following neonatal bacterial meningitis have not improved significantly over the past 30 years. New strategies are required to prevent infection occurring. It is hoped that strategies including maternal vaccination, improved infection control practices and more effective strategies for chemoprophylaxis in at-risk pregnancies and infants will reduce the incidence of this potentially devastating disease in the coming years (Galiza and Heath 2009).

SUBACUTE OR CHRONIC AND GRANULOMATOUS BACTERIAL MENINGITIS

Tuberculosis Meningitis

Tuberculosis is caused by infection due to *Mycobacterium tuberculosis* (*M. tuberculosis*). Over the past two decades, global incidence, prevalence and mortality from tuberculosis have been slowly falling. Estimating the burden of both latent and active tuberculosis infection in children is difficult as there are limitations in the performance of current diagnostic methods, with diagnosis often being presumptive. However, in 2012, WHO estimated that there were approximately 530,000 cases of tuberculosis in children and 74,000 deaths from the disorder in HIV-uninfected children worldwide. Multi-drug-resistant tuberculosis is increasingly reported, with an isolate from a child infected with tuberculosis being just as likely to be drug resistant as that from an adult (WHO 2013). In one region of South Africa, tuberculosis meningitis (TBM) is now the most common form of bacterial meningitis in children (Wolzak et al. 2012). In the UK in 2012, the reported rate of tuberculosis in children under 5 years was 4.1 per 100,000. From all ages, overall rates of drug resistant isolates have shown a gradual upward trend (PHE 2014a, b). In the United States during 2005–6, the estimated rate of tuberculosis in children under 5 years of age was 2.57 per 100,000 (Pang et al. 2014). Following exposure to tuberculosis infection, in the absence of preventive treatment, infants are particularly vulnerable to tuberculosis disease, especially disseminated disease (e.g. miliary tuberculosis and TBM). Examining reports from the pre-chemotherapy era, it is estimated that following primary infection, 30–40% of children under 1 year of age progress to pulmonary disease and 10–20% progress to miliary disease or TBM. TBM was present in 30% of children who presented with tuberculosis before 2 years of age (Marais et al. 2004). It is almost universally fatal if left untreated and even with current strategies, mortality is high and neurological outcomes severe, delays in recognition and treatment being associated with worse outcome (Chiang et al. 2014).

**Pathology and pathogenesis of tuberculous meningitis**

Most cases of mycobacterial meningitis are caused by *M. tuberculosis*. A small proportion is caused by zoonotic infection with *Mycobacterium bovis*, which may be associated with ingestion of unpasteurised milk (Durr et al. 2013). Occasional cases are due to atypical mycobacteria (Flor et al. 1996). Cases have been observed attributable to disseminated Bacillus Calmette-Guérin (BCG) infection following immunisation in immunodeficient children (Pang et al. 2014). Infection with rare or unusual mycobacterial species in children should be investigated for underlying immunodeficiency including specific genetic susceptibility defects such as those involving interferon gamma and IL12 receptor defects (Levin et al. 1995; Newport et al. 1996; Al-Muhsen and Casanova 2008; Haverkamp et al. 2014).

The majority of cases of TBM are preceded by a primary focus in the lung following inhalation of the acid-fast bacillus. Progression from this primary focus then occurs, with dissemination of bacilli through lymphatics and through haematogenous routes to distant sites. The exact pathogenesis has been recently debated. For many years a two-step model of TBM pathogenesis was presumed, involving initial haematogenous spread of bacilli to the brain or meninges with a tuberculous focus known as a ‘Rich focus’ then developing and subsequently discharging into the subarachnoid space followed by caseating necrosis. This process was proposed to be separate to that involved in miliary tuberculosis (Rich and McCordock 1933; Starke 1999; Donald et al. 2005; Thwaites et al. 2013). This proposal has recently been called in to question and it is currently thought that it is more likely that miliary tuberculosis and TBM (at least in children) result from the same process of haematological dissemination followed by establishment of discharging foci of tuberculosis infection in tissues, potentially including the CNS with consequent TBM. The reason why some children develop miliary tuberculosis and others TBM is yet to be elucidated (Donald et al. 2005). Occasionally, infection can spread directly from sites close to the CNS including middle ear, vertebrae or skull (Starke 1999). In adults, a polymorphism in *TLR2* has been shown to be associated with development of TBM, highlighting the possible role of innate immunity in susceptibility to and/or control of disseminated infection (Thuong et al. 2007). A relationship between *M. tuberculosis* genotype and TBM phenotype, again in adults, has also been demonstrated (Thwaites et al. 2008). However, a study in children failed to show a relationship between genotype and TBM phenotype (albeit in a different ethnic population) (Maree et al. 2007).

The infection generates a cascade of inflammatory mediators, with secondary generation of a thick exudate that settles along the base of the brain (Fig. 11.6). This in turn induces a vasculitis with secondary thrombosis of adjacent arteries and veins, resulting in embolisation and infarction, particularly in the small lenticulostriate vessels supplying the basal
ganglia, as well as in the cerebral cortex, pons and cerebellum (Poltera 1977; Starke 1999; Rock et al. 2008). Over time, the exudate fills the basal cisterns, resulting in entrapment of cranial nerves and blockage of CSF drainage pathways resulting in secondary hydrocephalus (communicating or obstructive). Rich foci can enlarge to form CNS tuberculomata (Wallace et al. 1991; Buonsenso et al. 2010) or tuberculous abscesses (du Plessis et al. 2007; Buonsenso et al. 2010). Tuberculous encephalopathy has previously been described associated with diffuse, predominate white matter brain injury, possibly as a result of a post or para-infectious allergic encephalitis (Dastur 1986). However, the existence of tuberculous encephalopathy has recently been debated (Lammie et al. 2007; Kim et al. 2011). More recent reviews of the wider literature suggest that cases previously grouped together as tuberculous encephalopathy may be heterogeneous in nature and that tuberculosis may be an uncommon cause of disorders such as acute disseminated encephalomyelitis (ADEM) and acute haemorrhagic leucoencephalopathy, rather than a cause of a distinct entity of tuberculous encephalopathy (Lammie et al. 2007).

Vaccination
The efficacy of BCG vaccine is highly variable, depending on age, vaccine efficacy endpoint and geographical location. A recent systematic review has looked at this in detail (Mangtani et al. 2014). Protection against pulmonary disease is variable, protection being greatest when vaccine was administered in infancy or childhood. The vaccine is more effective in settings further from the equator. Protection against TBM and miliary tuberculosis (approximately 85% efficacy) was confirmed especially in neonates and in children when stringent tuberculin testing was employed (to exclude existing tuberculosis infection) (Mangtani et al. 2014). Novel vaccination strategies are currently being investigated including strategies to boost the existing response to BCG (with viral vectored or protein adjuvant boosting) or to replace BCG (priming vaccines) (Mangtani et al. 2014).

Clinical manifestations of tuberculous meningitis
The clinical manifestations of TBM are extremely variable (Table 11.7) (Idriss et al. 1976) so that the diagnosis may be very difficult. Virtually any neurological picture can be seen. TBM usually progresses over three successive stages, which if untreated results in death in 3–4 weeks. The nature of these stages is influenced by the age of the child. They have been defined by the UK Medical Research Council (MRC 1948; Starke 1999). All stages may involve fever. Stage 1 is characterised by personality change, listlessness, irritability and loss of appetite. Stage 2 involves progression to development of neurological signs and signs of raised intracranial pressure including drowsiness, neck stiffness, cranial nerve palsies, vomiting,

| Table 11.7 Clinical features at presentation of children with tuberculous meningitis |
|--------------------------------------|-----------|
| Nuchal rigidity                     | 77%       |
| Apathy                              | 72%       |
| Fever                               | 47%       |
| Vomiting                            | 30%       |
| Drowsiness                          | 23%       |
| Headache                            | 21%       |
| Coma                                | 14%       |
| Papilloedema                        | 9%        |
| Convulsions                         | 9%        |
| Facial palsy                        | 9%        |
| VIth nerve palsy                    | 9%        |
| IIIrd nerve palsy                   | 9%        |
| Hemiparesis                         | 5%        |
| VIIIth nerve involvement            | 2%        |
| Diabetes insipidus                  | 2%        |

Data from Idriss et al. (1976).
focal or generalised convulsions. In younger infants, stage 2 may involve increasing head circumference and bulging fontanelle. Hemiplegia and movement disorders due to involvement of the basal ganglia are often observed (Gelabert and Castro-Gago 1988). Stage 3 involves progression to severe neurological deficits including coma (MRC 1948). Tuberculoma or tuberculous abscess presents as space-occupying lesions with accompanying neurological signs depending on location, with tuberculous abscess often having a more acute presentation than a tuberculoma (Kumar et al. 2002). Clinical features that have been shown to distinguish TBM from other forms of meningitis in children include duration of symptoms greater than 6 days, abnormal movements and focal neurological deficits (Kumar et al. 1999).

Atypical manifestations are common. Focal neurological deficits preceding the classic meningeal irritation have been reported and include field defects, aphasia, hemiparesis, monoparesis and abnormal movements. These may be associated with cerebral infarction (Starke 1999). Isolated high fever, severe convulsions and features mimicking intracranial tumours may be observed (Udani and Bhat 1974). Tuberculosis may also affect the spinal cord, manifest as fever and meningeval signs rapidly followed by paraplegia (du Plessis et al. 2008).

**Diagnosis of tuberculous meningitis**

The diagnosis classically rests on a history of exposure to persons with pulmonary tuberculosis, a positive tuberculin skin test or interferon gamma release assay (IGRA; see below) in association with a compatible clinical picture, chest X-ray changes, a CSF with lymphocytosis and elevated protein, and neuroimaging revealing the classic triad of infarction, hydrocephalus and basal enhancement. However, in practice diagnosis in children is often extremely difficult.

Microscopy of CSF samples may allow detection of mycobacteria and confirm a diagnosis; however, in view of the paucibacillary nature of *M. tuberculosis*, especially in children, the diagnostic yield is low (Yaramis et al. 1998). Sensitivity can be increased through obtaining larger volumes of CSF; spending more time on microscopy (Thwaites et al. 2004) and CSF centrifugation (Stewart 1953). A modified Ziehl–Neelson staining method including a cytopin step has recently been shown to increase the sensitivity of CSF microscopy and allows clearer visualisation of the intracellular mycobacterium (Chen et al. 2012). Fluorescence staining has been shown to increase sensitivity in sputum and samples from other extrapulmonary sites (Steingart et al. 2006; Kumar and Chandra 2008) although direct evidence of its additional benefit in CSF samples is currently lacking.

Typical findings in CSF are raised protein, CSF pleocytosis with lymphocyte predominance, low glucose and raised opening pressure. Atypical findings are relatively common in children and these parameters should always be interpreted in the context of clinical history, examination findings and imaging (Starke 1999; Thwaites and Tran 2005; van Well et al. 2009). The sensitivity of tuberculosis culture of CSF in children with TBM is lower than that in adults (Yaramis et al. 1998; Starke 1999; van Well et al. 2009). Sensitivity can be increased by culturing centrifugation deposits from larger volumes of CSF; however, this is not always feasible in children (Thwaites et al. 2004). Culture times are prolonged and involve the use of both liquid and solid culture media. Mycobacterial growth indicator tubes (MGIT) can result in decreased time to detection of positive tuberculosis cultures. Microscopic observation of drug susceptibility (MODS) is a culture technique using liquid culture medium that has been demonstrated to also result in faster detection of positive cultures in adult TBM (Caws et al. 2007) and is a sensitive and more rapid technique for diagnosis of TBM in children (Tran et al. 2013). Culture from sites other than CSF, including sputum, gastric washings, bone marrow aspirate, lymph node biopsy, can also be of use in diagnosing CNS disease (Doerr et al. 1995; van Well et al. 2009).

Various non-culture techniques for detection of the presence to *M. tuberculosis* and to assess drug resistance are now available. Nucleic acid amplification tests have been shown to have a wide range of sensitivities and specificities (Pai et al. 2003) and therefore cannot be used to rule out TBM but their rapid turnaround times can be useful in rapid diagnosis of TBM (Marais and Pai 2007). Xpert MTB/RIF (Cepheid, CA, United States) is an automated nucleic acid amplification test based on real-time PCR which is increasingly being used across the globe for detection of *M. tuberculosis* and rifampicin resistance (a surrogate of multidrug resistance) in a range of clinical specimens. A study in adult patients found Xpert MTB/RIF to have a sensitivity of 95% and a specificity of 99% for diagnosis of TBM if large volumes of CSF were used (Nhu et al. 2014). A study in children comparing Xpert MTB/RIF and GenoType MTBDR plus showed a sensitivity of 93% and 26% respectively for detection of tuberculosis infection in CSF samples. Sensitivity of both assays used together in combination with culture resulted in a sensitivity of 56% with 98% specificity (Solomons et al. 2015). Measurements of adenosine deaminase and interferon gamma in CSF samples have shown some promise in distinguishing TBM from other forms of meningitis but have not yet entered widespread clinical practice (Mishra et al. 1996; Juan et al. 2006; Gupta et al. 2010a; Tuon et al. 2010).

The tuberculin skin test (Mantoux) is often negative in the context of active tuberculosis disease and interpretation may also be complicated by a history of BCG vaccination. Interferon gamma release assays (IGRA) are an in vitro method by which production of interferon gamma by lymphocytes is measured in response to stimulation with antigens that are more specific to *M. tuberculosis* than those used in the tuberculin skin test. They have good sensitivity and specificity for detection of latent tuberculosis infection in adults; however, their utility compared to tuberculin skin test in children in various contexts is controversial. A negative test should not be used to rule out active tuberculosis infection in children and they cannot be used to differentiate between latent infection and active disease (Machingaidze et al. 2011; Sollai et al. 2014). Attempts have been made to perform IGRA directly
on CSF samples (Park et al. 2012), but the higher volumes of CSF that may be needed to achieve adequate sensitivity may reduce the potential utility of this technique in pediatric samples. The search for novel biomarkers to help diagnose tuberculosis infection and to distinguish latent tuberculosis infection from disease is ongoing (Maertzdorf et al. 2012) and results of studies investigating RNA transcriptome in whole blood, for example (Anderson et al. 2014), show promise.

CT and MRI are not essential but can be a very useful adjunct in the diagnosis and assessment of TBM. Characteristic findings that support a diagnosis of TBM include the presence of hydrocephalus (present in approximately 80% of children), basal meningeal enhancement (present in approximately 75% of children), infarctions, tuberculomata and pre-contrast basal hyper-density (Wallace et al. 1991; Andronikou et al. 2004; Marais et al. 2010) (Fig. 11.7a).

MRI may be more sensitive and accurate in detecting changes associated with TBM including basal meningeal enhancement and infarctions (Pienaar et al. 2009). Diffusion-weighted imaging has confirmed that areas of ischaemia and necrosis in the brain stem (van der Merwe et al. 2009) and border-zones (Omar et al. 2011) are relatively common in children with TBM. MRI has also been used to demonstrate that a miliary pattern of leptomeningeal infection is present in a high proportion of children with TBM (Janse van Rensburg et al. 2008) (Fig. 11.7b). Magnetic resonance angiogram (MRA) can also be of use in assessing the extent of vascular involvement. A study involving adults and children with TBM found abnormalities on MRA in half of patients, with around 60% of patients having corresponding infarctions (Kalita et al. 2012).

Tuberculomata or tuberculosis abscesses may be present in isolation or in addition to TBM and have characteristic findings on CT and MRI depending on the stage in their development at which imaging is performed (Wallace et al. 1991; Bernaerts et al. 2003; du Plessis et al. 2007). A tuberculoma appears on CT or MRI as a round mass, sometimes with a necrotic, clear centre (ring lesion). They may be polycystic in contour and behave as space-occupying lesions (Fig. 11.7). Calcification is common (Wallace et al. 1991; Bernaerts et al. 2003).

In view of the difficulties in diagnosing TBM, and in an effort to standardise disease definitions, diagnostic criteria for possible, probable and definite TBM have been proposed. This involves scoring of a number of clinical, CSF and imaging criteria which are totalled giving a cumulative score which is indicative of the likelihood of M. tuberculosis being the cause of a case of meningitis (Marais et al. 2010).

**Differential diagnosis of tuberculous meningitis**

The differential diagnosis of TBM includes a large part of the neurological pathology of childhood, in particular other lymphocytic meningitides and aseptic meningitis (see Table 11.3). Neoplastic meningitis that occurs in cases of metastatic tumours, especially germinomas, ependymomas, choroid plexus tumours, medulloblastomas and sarcomas, may mimic TBM. Partially treated bacterial meningitis may share many of the clinical features of TBM and result in similar laboratory test results. In cases where doubt exists, antituberculous drug treatment should be started and discontinued later, once an alternative diagnosis has been confirmed and tuberculosis has been excluded.

**Treatment of tuberculous meningitis**

National and international guidelines vary in terms of recommended first-line antituberculous medication combinations, duration of treatment, guidance on the use of adjunctive steroid
therapy and duration of treatment. Robust randomised controlled trial evidence to guide best practice is sparse. In general recommended treatment involves an initial short course of four antibiotics (isoniazid, rifampicin, pyrazinamide, ethambutol) for 2 months followed by an extended course of a combination of two drugs (isoniazid, rifampicin) to complete a year of therapy (WHO 2006, 2010b; Thwaites et al. 2009; NICE 2011; AAP 2012). Ethambutol can produce optic neuritis (Donald et al. 2006), so visual acuity should be monitored. Isoniazid can induce a peripheral neuropathy, and can be prevented by the administration of pyridoxine (though guidelines again vary on which groups require prophylactic pyridoxine (WHO 2006, 2010b; Moore et al. 2009; Thwaites et al. 2009; NICE 2011; AAP 2012). Some authors currently recommend 6 months of a four-drug combination including ethionamide in place of ethambutol in view of better CSF penetration of ethionamide (Moore et al. 2009; Thwaites et al. 2013). All of the major guidelines recommend use of steroids (prednisolone or dexamethasone) in the first month of therapy followed by a reducing dose over the following 2–4 weeks (WHO 2006, 2010b; Moore et al. 2009; Thwaites et al. 2009; NICE 2011; AAP 2012). Recommended dosing of antituberculous drugs also varies between guidelines with suggested regimens aiming at optimum drug concentrations in CSF (WHO 2006, 2010b; Moore et al. 2009; Thwaites et al. 2009; Donald 2010; NICE 2011; AAP 2012; Principi and Esposito 2012). Second-line drugs that can be used in the context of suspected or confirmed resistant tuberculosis infection or when the oral route of administration is not possible include cycloserine, streptomycin, amikacin, moxifloxacin and levofloxacin (WHO 2006, 2010b; Moore et al. 2009; Thwaites et al. 2009; NICE 2011; AAP 2012; Principi and Esposito 2012). Resistance to any of these antibiotics can develop when they are given alone, and administration of several drugs simultaneously largely prevents the emergence of resistant strains (Iseman 1993). With the increasing emergence of multi-drug-resistant TB, determination of the sensitivity of the organism, if cultured, should be obtained where possible and treatment adjusted accordingly. When this information is not available, resistance information from an isolate studied in an index case can help guide empirical treatment decisions. The management of suspected or confirmed drug-resistant TBM in children is complex. Guidance on strategies for management of these cases is available, and is ideally provided by clinicians with experience in the issues involved in the use of second-line drugs in children, specifically relating to toxicities, dosing and CSF penetration (Donald 2010; Thwaites et al. 2013; Schaaf et al. 2014). Adjunctive treatment with thalidomide has demonstrated some benefit (Schoeman et al. 2006) but requires further study before recommendations can be made for routine clinical use (Buonsenso et al. 2010).

Indications for surgical treatment include hydrocephalus, or tuberculous abscess (Rock et al. 2008; Thwaites et al. 2013). Hydrocephalus is common in children especially in later stages of the disease. It can be communicating or non-communicating. Communicating hydrocephalus can often be successfully treated medically [e.g. with furosemide and acetazolamide (Schoeman et al. 2000)]. If medical treatment fails or in non-communicating hydrocephalus, ventriculoperitoneal shunting is indicated (Lamprecht et al. 2001). Tuberculomata very rarely require surgical management with current medical therapies. Tuberculous abscesses more frequently require surgery ranging from simple aspiration to total excision (Kumar et al. 2002).

**Prognosis of Tuberculous meningitis**

TBM in children has very poor outcomes. A systematic review and meta-analysis has compiled data on treatment outcomes...
in children with TBM between 1952 and 2012. Information on outcomes for 1636 children was analysed. Risk of death was 19.3% (95% confidence intervals 14.0–26.1) and probability of survival without neurological sequelae was 36.7% (95% confidence intervals 27.9–46.4). Risk of neurological sequelae in survivors was 53.9% (95% confidence intervals 42.6–64.9). Outcomes were poorer in TBM diagnosed in stage 3 disease than in earlier stages (Chiang et al. 2014). Multi-drug-resistant TBM is also associated with worse outcomes than fully sensitive tuberculosis (Seddon et al. 2012). Neurodevelopmental outcomes have been shown to correlate with the distribution and extent of cerebral infarction, bilateral basal ganglia infarction having a particularly poor prognosis (Springer et al. 2009).

CHRONIC MENINGITIS

Chronic meningitis is a syndrome characterised by various combinations of fever, headache, lethargy, confusion, neck stiffness and vomiting, along with CSF pleocytosis and elevated protein that fails to improve over four weeks (Tan 2003). The main causes of this syndrome are infective and are shown in Table 11.3, but there is a wide differential and noninfectious aetiologies should always be considered (Ginsberg and Kidd 2008). A careful travel and exposure history as well as examination are important in identifying the aetiological agent and should guide focused, step-wise investigation (Seyd et al. 2009). Some of the causes of chronic lymphocytic meningitis are described in the next sections. They include conditions such as Lyme disease, neurobrucellosis and Cryptococcus neoformans meningitis. Chronic polymorphonuclear pleocytosis may be caused by infectious agents such as Nocardia spp. and Actinomyces spp., and a number of fungi (Peacock et al. 1984).

INTRACRANIAL ABSCCESS AND EMPYEMA

Cerebral Abscess

Brain abscess is an uncommon but life-threatening condition in children. Any age can be affected. A recent case series of 118 children over 10 years from the UK reported a bimodal age distribution with most cases occurring in children under 2 years, or aged between 9 and 15 years (Felsenstein et al. 2013). Other case series have shown a similar age distribution (Wong et al. 1989) or a peak in early teenage years (Leotta et al. 2005). The responsible organisms gain access to the brain most commonly via the haematogenous route from a distant focus or by direct extension from a nearby focus such as otitis media, dental infection, mastoiditis or sinusitis, or a septic thrombocephlebitis of bridging veins. Abscesses can also complicate meningitis. One major predisposing factor in children is cyanotic congenital heart disease, although this seems to be a less prominent factor in more recent years (Goodkin et al. 2004; Leotta et al. 2005; Shachor-Meyouhas et al. 2010; Cole et al. 2012; Felsenstein et al. 2013). Abscesses that result from bacteraemia are often multiple, and are often found in the distribution of the middle cerebral artery and at the border between white and grey matter (Bakshi et al. 1999; Yogev and Bar-Meir 2004). Abscesses secondary to focal infections arise at adjacent sites through direct invasion (e.g. frontal, temporal, cerebellar) (Saez-Llorens 2003). Brainstem abscesses are uncommon.

A microbiological diagnosis may be achieved through direct culture or PCR from the abscess site or from culture of CSF, blood, or adjacent sites (e.g. mastoid, sinus). The most common causal organisms are streptococci (especially Streptococcus anginosus group). A wide range of other organisms are implicated including H. influenzae, S. pneumoniae, S. aureus, Enterococcus spp. and Enterobacter spp. Mixed growth is common. Citrobacter spp. are associated with abscesses during the neonatal period (Chowdhry and Cohen 2012). Anaerobes are involved in a minority of cases, but the possibility of anaerobic infection should guide empiric antibiotic therapy (Goodkin et al. 2004; Leotta et al. 2005; Shachor-Meyouhas et al. 2010; Cole et al. 2012; Felsenstein et al. 2013). A similar range of organisms is found in the context of immunodeficiency with the addition of opportunistic infections including fungi, Toxoplasma gondii and Nocardia spp. (Chow et al. 2005; Alsultan et al. 2006; Voegele et al. 2013).

The initial stage of an abscess is septic encephalitis or cerebritis, which consists of an oedematous area with softening and congestion of the brain. Neutrophils accumulate, and microglial and astrocyte activation is evident with the elaboration of numerous pro-inflammatory cytokines (Kielen 2004). Over time, the centre becomes liquefied thus forming the abscess cavity, while a wall develops, initially thin, and then becoming a thick, firm capsule. Initially composed of inflammatory granulation tissue, the capsule becomes fibrous. Marked oedema surrounds the abscess and is responsible in part for the high ICP that is prominent in cases of brain abscess (Frazier et al. 2008).

CLINICAL MANIFESTATIONS OF CEREBRAL ABSCESS

The clinical manifestations of brain abscess depend on a number of factors including age of child, virulence of infecting organism, presence of immunodeficiency, site of abscess, source of infection and speed of progression. Symptoms are frequently nonspecific in the early stages of the disease. Headache, fever, decreased consciousness, seizures and focal neurological signs are relatively common presenting features. Neck stiffness and cranial nerve signs are less common. Infants may present with increasing head circumference (Wong et al. 1989; Leotta et al. 2005; Shachor-Meyouhas et al. 2010; Felsenstein et al. 2013).

DIAGNOSIS OF CEREBRAL ABSCESS

Blood cultures are frequently negative (Saez-Llorens 2003; Yogev and Bar-Meir 2004; Frazier et al. 2008; Cole et al. 2012) and inflammatory markers are not always raised (Frazier et al. 2008; Cole et al. 2012). Lumbar puncture is often contraindicated due to clinical presentation; however, if done it
reveals nonspecific changes such as pleocytosis, raised protein and low glucose (Wong et al. 1989; Tattevin et al. 2003; Frazier et al. 2008). The diagnosis of brain abscess is confirmed on neuroimaging (Fig. 11.9). Bacterial culture of samples obtained during surgical intervention can increase the chances of identifying causative organisms, although these samples may also be culture negative. Broad-range bacterial PCR (16S ribosomal) can aid in identification of organisms from culture negative samples (Al Masalma et al. 2009).

Cranial ultrasound may be useful in the neonatal period. MRI is superior to CT and is considered the preferred imaging technique. At the initial stage, neuroimaging may show only localised ill-defined hypodensity with a mass effect. Later, a rim of contrast enhancement appears and becomes thicker with the passing of time. MRI at this stage classically reveals a round mass with strong peripheral contrast enhancement and surrounding vasogenic oedema. The capsule may be hyperintense on T1 and hypo-intense on T2-weighted images. Multiple abscesses and multilocular abscesses can be visualised. Differential diagnosis includes cavitated brain tumours, tuberculomata, focal ischaemic lesions, intracerebral cysts and Schilder disease (see Chapter 10). Diffusion-weighted MRI is a useful technique for differentiating abscess from neoplasm (Frazier et al. 2008; Nickerson et al. 2012). CT and MRI may also reveal sinus or mastoid pathology as a focus of infection. The EEG may be useful as it shows a good correlation between the location of the abscess and that of a focus of slow delta waves (Vignadndra et al. 1975).

**Management of Cerebral Abscess**

There are no randomised trials of management (surgical or medical). Treatment is therefore currently based on historical case series and expert opinion. Broad spectrum antibiotic therapy is the mainstay of treatment for the majority of brain abscesses, and alone can achieve complete resolution of the abscess if commenced early (although this is possible in a minority of cases). Surgical intervention is commonly indicated. Techniques such as stereotactic aspiration, craniotomy and endoscopic drainage may be used. Third generation cephalosporins and additional anaerobic cover with metronidazole are currently recommended for empirical treatment (with vancomycin added in cases following trauma or surgery). In all cases where an organism has not been isolated from either blood or other fluids (e.g. pus from sinuses/mastoid) a diagnostic aspiration through a burr hole using CT- or MRI-guided stereotactic aspiration is recommended. Subsequent therapy is guided by antibiotic sensitivity. Antibiotics should be maintained for at least 4–6 weeks and the patients carefully monitored by repeated imaging. Follow-up scans often continue to demonstrate ring enhancement for several weeks, with or without surgical puncture. Disappearance of the capsule on CT should be verified. If antibiotic therapy is not rapidly effective, or pressure effects are causing significant concerns, again surgical drainage by tapping through a burr hole should be performed. Removal of the capsule is not generally advised and is limited to patients in whom a residual cavity or large persistent hyper-intensity is present on late scans (Saez-Llorens 2003; Yogev and Bar-Meir 2004; Frazier et al. 2008; Shachor-Meyouhas et al. 2010; Cole et al. 2012; Felsenstein et al. 2013).

**Sequela of Cerebral Abscess**

Mortality rate of brain abscess in children is currently much lower than in early case series (Brouwer et al. 2014), ranging from 3.7–10% in recent case series (Leotta et al. 2005; Shachor-Meyouhas et al. 2010; Felsenstein et al. 2013). Mortality is higher in immunodeficient children (Felsenstein et al. 2013). Neurological sequelae are relatively common including seizures, motor deficits and hydrocephalus. In case series including children and adults, approximately 70% of patients with brain abscess have no or minimal neurological sequelae. (Goodkin et al. 2004; Leotta et al. 2005; Frazier et al. 2008; Felsenstein et al. 2013; Brouwer et al. 2014). Younger age and GCS ≤ 8 at presentation are associated with a worse outcome (Felsenstein et al. 2013). Neonatal abscesses are generally associated with a poor outcome, with neurological deficits being present in over two-thirds of the patients and residual epilepsy in over half the cases (Renier et al. 1988).

**Subdural Empyema**

Subdural empyema is an infectious collection of fluid accumulating between the dura and arachnoid, and most commonly occurs as a result of direct spread from sinuses (in...
Epidural Abscess

Epidural abscesses can affect the head and the spinal canal. Spinal epidural abscesses are uncommon and result from either haematogenous spread of bacteria from distant sites of infection, direct spread from adjacent sites or are iatrogenic following an invasive procedure. Infection is most frequently localised to the dorsal aspect of the cord. Although *Staphylococcus aureus* is by far the predominant causal organism, more unusual organisms and opportunistic infectious agents such as fungi and atypical mycobacteria may be isolated in individuals with comorbidity or underlying risk factors such as immunosuppression. Backache is the first manifestation, followed by neurological symptoms such as radicular pain and symptoms of spinal cord compression (Pradilla et al. 2009, 2010; Hawkins and Bolton 2013). The presenting symptoms and signs may be indistinguishable from those of transverse myelitis. Gadolinium-enhanced MRI is currently the investigation of choice for diagnosis. Lesions appear iso- or hypo-intense on T1 weighted images and hyperintense on T2 weighted images (Pradilla et al. 2009, 2010; Nickerson et al. 2012).

Owing to the rarity of this condition, there are no randomised trials to guide treatment practices. Ideally, blood cultures and samples from the site of infection should be obtained prior to commencing empiric antibiotic therapy. Antibiotics should provide broad Gram-positive and Gram-negative cover initially and then be tailored, once the causative organism is isolated and its antibiotic sensitivity is known. Management depends on whether there is evidence of cord compression. If there is no evidence of cord compression, surgery can be avoided and the abscess can be managed conservatively with 4–6 weeks of appropriate intravenous antibiotic therapy. If there is any evidence of cord compression, or a large loculated abscess is present, then urgent surgery is required. Medical management alone may also be appropriate in cases where there is a high risk of complications following surgery, for example in those with complete paresis for longer than 72 hours or those with extensive infection covering many spinal levels (Pradilla et al. 2009, 2010; Hawkins and Bolton 2013).

Intracranial epidural abscesses are also rare and most commonly result from direct spread of infection from sinuses. Symptoms may include fever, headache, nausea and vomiting. Infection can be polymicrobial including Gram-positive and negative, anaerobic and aerobic organisms and can co-exist with osteomyelitis. Empiric antibiotics should therefore provide cover for these organisms. MRI is the investigation of choice, showing a collection that is iso-intense to underlying brain parenchyma on T1 sequences and hyperintense on T2 with restricted diffusion on diffusion-weighted imaging (Pradilla et al. 2009; Nickerson et al. 2012; Nicoli and Makite 2014) (Fig. 11.10). Management includes a prolonged course of antibiotics (6 weeks minimum) and surgical drainage is often necessary (Pradilla et al. 2009).
Intramedullary Abscess

Intramedullary abscess is a rare condition resulting from either haematogenous spread or more commonly through a pre-existing congenital defect in the spinal cord. A review of all reported paediatric intramedullary abscesses noted that 89% of children presented with neurological deficits (paralysis, paraesthesiae, incontinence) (Simon et al. 2003). The diagnosis is best made with MRI, and organisms are varied, with *Staphylococcus* spp., *S. pneumoniae* and other *Streptococcus* spp., *E. coli* and *Proteus* spp. accounting for the majority (Morandi et al. 1999; Simon et al. 2003). Of the cases reported by Simon et al., 55% had single organisms, 17% mixed, and 28% were sterile (prior antibiotic therapy accounted for some of these). Treatment was surgical decompression followed by antibiotic therapy for, on average, 4–6 weeks. Mortality was around 10%. Neurological sequelae were common (Simon et al. 2003).

Infection and Inflammation of the Vertebræ and Disc Space

Vertebral osteomyelitis is often associated with a limp or other walking difficulty (Fernandez et al. 2000). Neurological complications occur in approximately 12% of patients (Fuchs et al. 2012). Discitis is an imperfectly understood condition which tends to affect younger children more than vertebral osteomyelitis. It can occur in the thoracic, lumbar or sacral spine, but is most common in the lumbar region in children under 5 years of age. Blood cultures may be positive but often these are organisms associated with ‘contaminated’ blood cultures; in many cases no organism is found and the infectious nature is not certain. Depending on the age of the child, presentation is variable, with the child either refusing to weight-bear or presenting with back, hip or abdominal pain (Fernandez et al. 2000). On examination, flexion of the spine may be limited with loss of lumbar lordosis. X-rays of the spine show narrowing of the disk-space in 80% of cases (Jansen et al. 1993). Radionuclide uptake is increased at the level of the lesion. The condition should be distinguished from vertebral tuberculosis (Forti’s disease). Most children improve with a 4–6-week course of antibiotics. Biopsy of the infected disc space is reserved for children refractory to antibiotics as cultures are usually sterile (Brown et al. 2001). Follow-up should include plain radiographs at regular intervals for 12–18 months to ensure resolution of the destructive process (Early et al. 2003).

Nonsuppurative Bacterial Infections

**Syphilis**

Congenital syphilis is by far the most common form of the disease in children, with acquired syphilitic meningitis being rare but nonetheless important to diagnose because of the effectiveness of therapy. Syphilis is caused by the spirochaete *Treponema pallidum*, which has the ability to invade the CNS in early and late forms of the disease and produce protean neurological manifestations. Congenital syphilis can be divided into early (under 2 years of age) and late infection. Neurological involvement is observed in approximately 20% of cases of early congenital syphilis. Neurosyphilis without neurological signs or symptoms (asymptomatic neurosyphilis) can occur and is common in children with other physical signs of congenital syphilis. Asymptomatic neurosyphilis can be diagnosed in a patient with clinical evidence of syphilis, CSF abnormalities of pleocytosis and reactive tests but no neurological signs. CNS infection can be present with normal CSF findings. Two possible forms of early neurosyphilis are observed (with some overlap): the first being acute syphilitic leptomenigitis, with classic signs of meningitis including vomiting and bulging fontanelle, and the second, chronic meningoarteriosclerotic neurosyphilis, presenting later in the first year of life with hydrocephalus, cranial nerve palsies and developmental regression. Ocular findings may include chorioretinitis, glaucoma and uveitis (Woods 2005).

Up to one-third of children with late congenital syphilis have asymptomatic neurosyphilis. Symptomatic neurosyphilis occurs rarely and is associated with VIIth nerve deafness, tabes dorsalis, neurovascular lesions and/or juvenile paresis (Chakraborty and Luck 2008). Juvenile paresis is characterised by altered consciousness as the initial symptom. Neurological signs set in later and include spasticity in half the cases and cerebellar signs in a quarter. Seizures occur in 30% of cases and optic atrophy in 10–15%. Deafness and multiple cranial nerve deficits may be present. Juvenile paresis should be distinguished from the much more frequent progressive metabolic or degenerative diseases.

Congenital neurosyphilis is diagnosed on the basis of a combination of clinical examination, specific (treponemal) and nonspecific (reactogenic or non-treponemal) serological tests on blood and CSF, CSF microscopy, CSF protein and glucose, neuroimaging and PCR (Michelow et al. 2002; Doroshenko et al. 2006). Treatment is with penicillin G for all stages of neurosyphilis.

**Leptospirosis**

Leptospirosis is a zoonotic disease caused by several spirochaetes of the *Leptospira interrogans* complex. Humans acquire disease through contact with infected fluids from rodents; for example, through broken skin when swimming in contaminated fresh water. Disease can range in severity from being asymptomatic to fulminant fatal infection. Initially, there is a systemic illness with chills, conjunctivitis and occasionally jaundice, renal failure and bleeding diathesis (Weil disease) followed by signs of meningeal irritation. Neurological manifestations of leptospirosis infection are rare but can include aseptic meningitis, encephalitis, intracranial haemorrhage, cerebellitis and myelitis; CSF can show lymphocytic pleocytosis and raised protein. Pathogenesis is mainly through a vasculitic process. The diagnosis is made with serology and treatment is with penicillin. Prognosis is generally good, although long-term sequelae occasionally occur. Prognosis is
worse if there are signs of encephalitis (Panicker et al. 2001; Mathew et al. 2006).

**Borrellosis (Lyme Disease)**

Lyme disease is endemic throughout North America, Europe and Asia. It is caused by the spirochaete from the *Borrelia burgdorferi* complex, and is transmitted from animal reservoirs to humans by tick vectors of the Ixodes genus. Most cases occur in late spring and summer, and occur commonly in the 5–14; year age group (CDC 2007, Feder 2008). Infection may be asymptomatic, cause only the specific rash (erythema migrans), or disseminate to many organs, including the CNS. The disease can be divided into three stages. Neurological involvement is reported in 5–10% of Lyme borreliosis (O’Connell 2010).

The first stage occurs 7–10 days after a bite, and is characterised by a rash known as erythema chronicum migrans, located in the area of the tick bite, that expands away from the bite. Minor constitutional symptoms may be present (Nau et al. 2009; Esposito et al. 2013a). The second stage, which occurs in 5–15% of patients, results from disseminated infection some weeks or months later. Systemic symptoms (e.g. arthrits, carditis, myositis) as well as both central and peripheral neurological involvement occur. The most common neurological abnormalities are cranial nerve involvement (particularly VIIth, but also Vth nerve palsy), papilloedema and aseptic meningitis (Shah et al. 2005), but peripheral neuropathy and radiculitis may also develop (Bingham et al. 1995). Facial palsy is unilateral in most cases (Lebech and Hansen 1992); bilateral involvement 8–15 days apart is highly suggestive of borrellosis (Angerer et al. 1993). In American Lyme disease (caused by *Borrelia burgdorferi sensu stricto*), meningeal signs are frequently observed but radiculitis is uncommon (Williams et al. 1990; Belman et al. 1993). The peripheral neuritis is usually asymmetrical, motor, sensory or mixed and involves the limbs or trunk (Pachner and Steere 1985; Hansen and Lebech 1992; Christen 1993). Rare manifestations include other cranial neuropathies, ataxia, chorea, encephalitis and symmetrical neuropathy of the Guillain–Barré type (Christen 1993) (Bingham et al. 1995) or transverse myelitis (Linsen et al. 1991). Pleocytosis is present in the majority of children with CNS involvement, and the CSF protein is raised (Feder 2008). The meningal reaction may become chronic, and Lyme disease is, with mumps, a major cause of prolonged aseptic meningitis, accounting for 11.7% of cases in the experience of Christen (1993). The spectrum of neurological disease observed in children is different from that observed in adults, facial nerve palsy and lymphocytic meningitis being the most common presentation while radiculopathy and peripheral neuropathy are relatively rare (Wilke et al. 2000; Feder 2008; Nau et al. 2009; O’Connell 2010).

The third stage of persistent infection may be observed in untreated patients from 6 months to many years after the initial infection. Skin lesions (acrodermatitis chronica atrophicans) may occur associated with peripheral neuropathy. The lesions are characteristic areas of skin thinning and prominent venous markings associated with pain, pruritis, hyperaesthesia or paraesthesia. Chronic progressive meningoencephalitis and cerebral vasculitis can occur. Joint manifestations, including chronic mono- or asymmetric oligo-arthritis, also occur in the third stage of the disease (Nau et al. 2009).

The controversial term ‘chronic Lyme disease’ has been applied to those with late stage untreated infection, those with permanent tissue damage despite adequate treatment and patients with persistent nonspecific subjective symptoms following adequate antibiotic treatment for Lyme (the latter being described as ‘post-Lyme syndrome’ by some). Due to problems with sensitivity and specificity of the laboratory diagnosis of Lyme disease, it is possible for chronic symptoms due to alternative diagnoses, following an initial incorrect diagnosis of Lyme, to be incorrectly labelled chronic Lyme disease (Hoppa and Bachur 2007; Bratton et al. 2008; Hassett et al. 2009; Hildenbrand et al. 2009).

The diagnosis of Lyme disease rests on the history (including travel and exposure history), clinical manifestations and laboratory demonstration of Borrelia infection. A history of tick bite is frequently missing, and erythema migrans occurs in only 67% of cases (Williams and Schned 1990; Williams et al. 1990). Three-quarters of cases occur from June to October. Serological diagnosis of Lyme may be made by IgG and IgM ELISA; however, the specificity is relatively low and confirmatory Western immunoblot testing is recommended as its specificity is higher. In early infection, serological assays are frequently negative (Hoppa and Bachur 2007; Bratton et al. 2008; Esposito et al. 2013a). Positive results are frequent in endemic areas but are not always related to current neurological disease (Halperin et al. 1989). PCR assay is of limited clinical use due to poor sensitivity (Pachner and Delaney 1993; Golightly 1997; Tuerlinckx et al. 2003; Hoppa and Bachur 2007; Bratton et al. 2008). Co-infection with other tick-borne infections may occur in geographical risk areas (Hoppa and Bachur 2007).

Abnormal MRI findings may include cranial nerve enhancement and punctate (or larger) areas of increased T2 signal in the white matter which may simulate multiple sclerosis (Belman et al. 1992; Hildenbrand et al. 2009). Atypical cases can masquerade as brainstem tumour (Curless et al. 1996). There is little evidence from paediatric studies on which to base treatment recommendations. Suggested treatment regimens for Lyme neuroborreliosis include intravenous ceftriaxone (for more severe disease), intravenous Penicillin G or oral doxycycline (in children >8 years) for 14–21 days (Mygland et al. 2010; O’Connell 2010; Esposito et al. 2013a). Treatment failures have resulted in a tendency for prolonged treatment (2–4 weeks), although no evidence is available to suggest that this is beneficial (Stanek and Strle 2003; Wormser et al. 2003).

**Brucellosis**

Brucella is a genus of Gram-negative organisms transmitted to humans from domestic animals, particularly cattle, in endemic
It is one of the most common zoonotic infections worldwide. Transmission occurs through ingestion of unpasteurised dairy products, eating or close contact with infected meat. It is endemic in a number of regions with highest incidence being reported in several Mediterranean countries (Greece, Italy, Spain), the Middle East, Turkey, Mexico and North Africa (Pappas et al. 2006). Involvement of the CNS in systemic brucellosis is rare, but meningitis can occur. The clinical presentation of brucellosis localised to the nervous system is diverse. Meningitis, meningoencephalitis, encephalitis, myelitis, radiculitis, cranial neuropathy and intracranial abscesses have all been reported. Diagnosis is usually made through serology or culture. Isolation of Brucella from the CSF is rare (Buzgan et al. 2010; Guven et al. 2013). There is no consensus on the treatment of neurobrucellosis. Treatment for 6 weeks to 6 months with two or three drug combinations is currently recommended including rifampicin plus doxycycline (in children over 8 years) or co-trimoxazole (in children under 8 years) alone or together with ceftiraxone or gentamicin initially (Pappas et al. 2006; AAP 2012; Guven et al. 2013). No evidence on duration of treatment is available. Length of antibiotic course should therefore be guided by clinical response. The prognosis is favourable except in patients with diffuse involvement of the CNS, in whom significant disability may persist.

**MYCOPLASMA INFECTIONS**

*Mycoplasma pneumoniae* is a common cause of respiratory tract infection in children. Infection can cause extrapulmonary manifestations including haematological, cardiac, CNS and musculoskeletal involvement. CNS disease is reported to occur in 0.1% of mycoplasma-infected patients (Koskiniemi 1993) and in 1–7% of hospitalised patients (Guleria et al. 2005). It is a common cause of encephalitis in children. In one large case series of paediatric encephalitis from California, mycoplasma was thought to be the causative organism in around 9%. Presenting symptoms included fever, lethargy, altered consciousness, focal neurological signs, seizures and hallucinations. Laboratory findings included CSF pleocytosis, raised protein and normal glucose. MRI abnormalities were present in approximately half of patients and the majority had abnormal EEGs (Christie et al. 2007). MRI changes frequently involve the basal ganglia. (Fig. 11.11). Culture of mycoplasma is technically difficult. Diagnosis can be made by assessing mycoplasma-specific IgM or by showing a rise in mycoplasma-specific IgG titre between acute and convalescent samples. The former lacks sensitivity and specificity whereas the latter does not help with acute diagnosis. Mycoplasma PCR on respiratory samples can increase sensitivity, but it does not prove mycoplasma to be the aetiological agent in the CNS (mycoplasma carriage is common in children). PCR on CSF samples is rarely positive (Guleria et al. 2005; Tsiodras et al. 2005; Christie et al. 2007; Yis et al. 2008; Meyer Sauteur et al. 2014). Measurements of mycoplasma antibodies in CSF and also cross-reacting antibodies against host neuron-associated glycolipids (GalC, GQ1b, GM1) have recently been proposed as additional diagnostic tools (Meyer Sauteur et al. 2014). The pathogenesis of mycoplasma encephalitis is unclear. Three main mechanisms have been proposed: direct neuroinvasion, neurotoxin, immune dysfunction or dysregulation. The former may occur in early-onset disease (Bitnun and Richardson 2015); the latter is the most likely mechanism in later or
delayed onset disease (Guleria et al. 2005; Tsiodras et al. 2005; Christie et al. 2007; Yis et al. 2008; Meyer Sauteur et al. 2014). There is limited data on treatment. Macrolide antibiotics are generally recommended, although their penetration of the blood–brain barrier is limited. In view of the proposed immune-mediated pathogenesis, immunosuppressive or immunomodulatory therapy with steroids or intravenous immunoglobulin (IVIg) respectively have also been used with variable outcomes (Guleria et al. 2005; Tsiodras et al. 2005; Christie et al. 2007; Yis et al. 2008). Long-term neurological sequelae have been reported in 20–60% of cases. Mortality is as high as 10% in some case series (Tsiodras et al. 2005).

Other neurological diseases that have been associated with mycoplasma infection include: aseptic meningitis, transverse myelitis, Guillain–Barré syndrome (GBS), cranial nerve/peripheral neuropathy, ADEM, stroke/cerebral infarction, bilateral thalamic necrosis, Bickerstaff’s brainstem encephalitis (Guleria et al. 2005; Tsiodras et al. 2005). Similar to mycoplasma encephalitis, many of these are thought to have an autoimmune component to their pathogenesis.

**LISTERIA MONOCYTOGENES INFECTION**

Infection by *L. monocytogenes* is observed mainly in neonates (early or late onset), occurring rarely in children outside of infancy unless immunocompromised (Posfay-Barbe and Wald 2009; Ben Shimol et al. 2012; Okike et al. 2013). Infection in older children should therefore prompt screening for immunodeficiency. It is transmitted through contaminated food such as milk and soft cheese. It can produce meningitis or a rhomboencephalitis with formation of multiple abscesses (Fig. 11.12). CSF examination shows a pleocytosis with often raised protein and low glucose. Diagnosis is made by direct CSF staining and culture. Recommended treatment is with ampicillin plus gentamicin (Klein et al. 1986; Ben Shimol et al. 2012).

**BARTONELLA HENSELAE INFECTION (CAT-SCRATCH DISEASE)**

Cat-scratch disease is a self-limiting illness, caused by *Bartonella henselae*, commonly affecting children and young adults. It has a worldwide distribution. In typical cat-scratch disease a cutaneous papule develops 3–10 days after exposure to a scratch or bite from a kitten or cat. Regional lymphadenopathy then develops (1–3 weeks after inoculation), with associated fever and systemic symptoms such as malaise, anorexia, nausea and abdominal pain. It is one of the infectious agents found during investigation of ‘pyrexia of unknown origin’ in children. (Jacobs and Schutze 1998). Multisystem involvement is increasingly recognised. Neurological involvement is infrequent and includes encephalopathy in the majority of cases. Headaches, altered consciousness and seizures have all been documented. CSF findings are often normal but can show pleocytosis and raised protein. Meningomyeloradiculopathy, facial nerve palsy, GBS, transverse myelitis and cerebral arteritis have all been reported. Diagnosis is by serological testing or PCR. Lymph node biopsy may help confirm the diagnosis. There are no randomised trials to guide treatment practices; choice of antibiotics is based on case series. As cat-scratch disease is often self-limiting some would not recommend antibiotics, preferring supportive care alone. If using antibiotics, antibiotics that penetrate CSF such as rifampicin or doxycycline are recommended (Florin et al. 2008). In children younger than 8 years, azithromycin or co-trimoxazole can replace doxycycline although CNS penetration is not optimal.
OTHER RARE CAUSES OF CENTRAL NERVOUS SYSTEM INVOLVEMENT ASSOCIATED WITH BACTERIAL INFECTION

These include Legionella infection, which has been associated with epileptic seizures, encephalopathy and peripheral neuropathy, although as with mycoplasma, whether this is a direct effect of infection or an immune-mediated process is unclear (Heath et al. 1986). Whipple disease, although usually a disorder of adults, has very rarely been observed in children (Tan et al. 1995; Duprez et al. 1996). It is caused by Tropheryma whipplei and it has a rare, purely neurological form which can present in two main ways: either with multiple neurological symptoms and signs and multiple lesions on CNS imaging, or with a focal mass lesion with signs associated with the location of the lesion (Tan et al. 1995; Duprez et al. 1996; Louis et al. 1996; Panegyres et al. 2006). CNS imaging may also be normal; PCR on CSF may be positive. Neurological manifestations may also occur along with gastrointestinal and rheumatological symptoms and signs. No randomised trial evidence is currently available to guide treatment. Regimens including penicillin/streptomycin or co-trimoxazole have been suggested. Intravenous meropenem or ceftriaxone have also been used (Panegyres et al. 2006). Rickettsial disorders are rare in Western countries with the exception of Rocky Mountain spotted fever, which is frequent in the eastern United States and is responsible for a meningoencephalitic picture (Bell and Lascari 1970).

VIRAL INFECTIONS OF THE NERVOUS SYSTEM

ACUTE VIRAL SYNDROMES

Over 100 viruses are associated with CNS disease in humans, causing a spectrum of disease ranging from the most benign to the most lethal conditions. The mechanisms of CNS involvement are multiple and in many cases poorly understood. Most viruses invading the CNS are carried from their original portal of entry to the body, and their original place of multiplication (e.g., lymphoid tissue), by haematogenous dissemination. The characteristics of viruses and hosts that determine penetration into the CNS have been studied extensively and are still being actively explored. Two principal clinical syndromes are commonly encountered: meningitis and encephalitis or encephalomyelitis. Meningitis results from the haematogenous spread of the virus into the CSF, often through the choroid plexus. Some viruses can then replicate in the choroid plexus and this may explain the ease with which they are isolated from the CSF. Encephalitis or encephalomyelitis results from direct or indirect involvement of the brain tissue itself by viruses. In many cases of encephalitis tissue damage is not caused by direct viral invasion but by the host-generated inflammatory response. Other acute neurological disorders occurring in the course of a proven or suspected viral infection have no inflammatory manifestations and are better regarded as para-infectious encephalopathies.

The epidemiology of viral infections is constantly evolving as novel pathogens emerge, and globalisation, migration and climate change expand the range of known agents. Arboviruses including Japanese encephalitis virus, West Nile virus and dengue are particularly important emerging infections. Other agents, including influenza A and B and enteroviruses, have the capacity to mutate into novel pathogenic strains causing local epidemics of neurological disease. Clinicians should keep abreast of local trends in formulating their differential diagnosis for children with CNS infection.

Improvements in identification of CNS viral infection have been driven by advances in molecular diagnostics, including increasingly sensitive and rapid multiplex PCR techniques, and also by MRI. In spite of these, in the majority of cases of presumed viral CNS infection no pathogenetic organism can be identified. Beyond supportive care, treatment options remain unsatisfactory for most viruses. Novel approaches including viral replication inhibitors and immunomodulatory therapy are the focus of ongoing research.

Any clinical classification of viral CNS disease is difficult and, to some extent, arbitrary. Many viruses can produce the whole gamut of aseptic meningitis, post-infectious encephalitis, primary encephalitis and acute encephalopathy. In this section, we focus first on the presenting syndromes of viral-associated CNS disease – each being caused by a wide range of viral agents – and then on the features of specific organisms.

Viral Meningitis

Aseptic meningitis is defined as inflammation of the meninges in the absence of bacterial growth in the CSF. In the era of conjugate vaccinations, which have greatly reduced the incidence of bacterial disease (especially in older children), up to 96% of meningitis in highly immunised populations is now aseptic (Nigrovic et al. 2007). The majority of cases with an identifiable cause are due to viruses (Sadarangani et al. 2015). This section concerns viral meningitis in the absence of parenchymal involvement (encephalitis). Viral meningoencephalitis is considered separately.

Pathophysiology of Viral Meningitis

Viruses enter the body via various mechanisms but viral infection of the meninges and CSF usually occurs following haematogenous dissemination of the virus, either during primary viraemia or later following further viral replication in other organs. Penetration of the blood–brain barrier is usually via the choroid plexus. Some viruses grow in the choroid
plexus itself and so are readily isolated from the CSF (e.g. echovirus, coxsackie virus). Penetration of the CNS via retrograde transport along cranial or other nerves may also occur for some of the herpes viruses and enteroviruses. The inflammatory response to viral invasion of the meninges is dominated initially by polymorphonuclear leukocytes and later by monocytes and lymphocytes.

**Epidemiology of Viral Meningitis**

Viral infection of the CSF can occur at any age but the majority of cases occur in children younger than three years, with a substantial proportion of these in the first two months of life (Nigrovic et al. 2013). A retrospective study of 506 Greek children with aseptic meningitis reported an overall incidence of 17 per 100,000, ranging from 26 per 100,000 in 1–5-year-olds to seven per 100,000 in teenagers (Michos et al. 2007). Cases occurred more commonly in summer and there was a male preponderance of 1.8:1. A multicentre Canadian study reported 802 paediatric cases of aseptic meningitis over a two-year period, resulting in 673 hospital admissions, with a 1.5:1 male preponderance and a marked summer peak associated with an enterovirus outbreak (Lee et al. 2006).

Enteroviruses are by far the most common aetiologic agent in aseptic meningitis. Enteroviral RNA was found in 49% of children tested in the Greek cohort and 54% of the Canadian cohort (Lee et al. 2006; Michos et al. 2007). In the UK, enteroviruses make up 52% of all laboratory-proven viral meningoencephalitis; the proportion is 92% in those aged less than 3 months, or 77 cases per 100,000 live births (Kadambari et al. 2014). Of aseptic meningitis without encephalitis, enteroviruses account for 77–92% of cases in which a causative agent is identified (Berlin et al. 1993; Rotbart 1995; Sadarangani et al. 2015). Echoviruses (e.g. serotypes 4, 6, 9, 11, 14, 16, 18, 20 and 30) are responsible for up to two-thirds of enterovirus meningitis (Lee et al. 2006) with group B coxsackie viruses (serotypes 1–5) making up most of the remaining cases. Other causative serotypes for meningitis include coxsackie A (e.g. 7, 9 and 25) and occasionally polioviruses. Some (e.g. coxsackie B5, echovirus 6, 9 and 30) are especially associated with meningitis epidemics, while others (coxsackie A9, B3 and B4) are mostly endemic.

Other less commonly isolated viral agents include arboviruses, arenaviruses (e.g. lymphocytic choriomeningitis virus), adenoviruses, herpes viruses, retroviruses (e.g. HIV), paramyxoviruses (e.g. mumps, measles), influenza, parechoviruses and parvovirus. The spectra of neurological illnesses caused by these agents are detailed in the relevant organism entries in this chapter. A recent UK study found human herpes virus 6 (HHV-6) and parvovirus to be the most common non-enteroviral causes although the overall numbers were small (Sadarangani et al. 2015). The UK Childhood Meningitis and Encephalitis Study (ChiMES) is an ongoing cohort study (UKCRN 14206) that should further expand our understanding of local epidemiology.

**Clinical Features of Viral Meningitis**

The onset of viral meningitis is usually acute. It is sometimes preceded by a short gastrointestinal or respiratory prodrome; there may be a history of similar symptoms among family members or other close contacts. In the Greek cohort (defined by CSF pleocytosis, negative bacteriology and subsequent course consistent with aseptic meningitis), the most common symptoms at admission were fever (98%), headache (94%), vomiting (67%), neck stiffness (60%), lethargy or irritability (46%), anorexia (40%), rash (9%), symptoms of upper respiratory tract infection (4%) and seizures (2%) (Michos et al. 2007). Nonspecific presentations with fever, rash, diarrhoea and/or cough occur more commonly in younger children; symptoms with greater specificity for CNS infection (headache, vomiting, neck stiffness, photophobia) were observed in only 55% of under-5s in the Canadian cohort, compared to 99% of over-5s (Lee et al. 2006). Brief episodes of obtundation or delirium may occur in a few patients but convulsions are unusual. Neurological examination is negative except for neck and back stiffness. The presence of persisting encephalopathy or neurological signs is suggestive of meningoencephalitis (see Viral Encephalitis section). Clinical features associated with specific causative agents are detailed in the relevant organism entries later in this chapter.

**Diagnosis of Viral Meningitis**

The focus of diagnostic efforts in meningitis should be on exclusion of bacterial causes. There is considerable overlap of symptomatology between viral and bacterial meningitis; clinical prediction rules are not able to reliably exclude bacterial causes on the basis of signs and symptoms alone (Kulik et al. 2013). The most important diagnostic test is the lumbar puncture and failure to undertake a lumbar puncture can significantly compromise patient management. Before embarking upon lumbar puncture, clinicians should review the contraindications listed in Table 11.1 and also consider the accompanying advice regarding pre-lumbar puncture neuroimaging in Clinical Manifestations and Diagnosis in the Acute Bacterial Meningitis in Infants and Children section.

CSF white cell count and protein are the most useful immediately available parameters for differentiating bacterial from viral causes of meningitis (Sadarangani et al. 2015), but all CSF interpretation should be undertaken in light of the overall clinical context. The typical viral picture of a lymphocytic pleocytosis with little or no elevation in protein and normal glucose does not always apply; polymorphonuclear leukocytes may predominate in the first 12–48 hours of illness (Amir et al. 1991), and protein and glucose levels may be abnormal in 45% and 84% of cases respectively (Lee et al. 2006). Nor should normal or near-normal CSF parameters (see Table 11.2 for reference values) be regarded as excluding a diagnosis of viral meningitis; up to 19% of proven enterovirus meningitis cases have normal CSF white cell counts, including up to 42% of infants aged less than 2 months (Sawyer...
C-reactive protein (Sadarangani et al. 2015), procalcitonin (Lee and Davies 2007) or neutrophil count should prompt consideration of bacterial over viral meningitis.

In the absence of bacterial growth in the CSF, the differential diagnosis of aseptic meningitis is broad and includes partially treated bacterial infection, atypical bacteria (e.g. Borrelia
been reported in up to 12% of cases (Lee et al. 2006). MRI hydrocephalus, ventriculomegaly and focal hypodensity have been superseded by molecular diagnostic testing using PCR (Box 11.1). PCR panel should include enteroviruses, herpes viruses and (in those under 3 years) parechoviruses, with further tests as indicated by foreign travel, contact history and clinical presentation. Additional CSF can be stored for further tests if required; for example, following discussion with the virologist or paediatric infectious disease specialist.

The sensitivity and specificity of CSF PCR for enterovirus meningitis is estimated to be close to 100% (Rotbart et al. 1997). If enterovirus is detected, the risk of co-infection with a bacterial agent is very low. In one cohort none of 735 enterovirus-positive children had bacterial growth in the CSF or blood (Nigrovic et al. 2010). In another cohort, none of 150 enterovirus-positive children had bacterial growth, although two had bacteria detected by CSF PCR (one Neisseria meningitidis and one Streptococcus pneumoniae) (Basmaci et al. 2011). One of these two had been pre-treated with antibiotics and the other was immunosuppressed; a more extensive diagnostic workup is required in such patients.

Viral isolation from other sites is helpful as an adjunct to CSF analysis. These could include urine, blood and stool samples, nasopharyngeal aspirates, and swabs of the oropharynx and rectum, depending on the clinical presentation. Stool and serum samples are useful if enterovirus is suspected (Lee and Davies 2007), and vesicle fluid especially so, as it is always indicative of acute infection (unlike samples from most other sites, which may represent chronic carriage) (Ooi et al. 2010). Serological virus-specific antibodies may be helpful in some cases; for example, where a long period has elapsed since onset of symptoms (Sauerbrei and Wutzler 2002), although the false positive rate is high in neurotropic viruses with high seroprevalence in the general population; paired acute and convalescent samples are usually required for a meaningful result. Even in the era of molecular diagnostic testing, no causative pathogen is identified in half or more cases of aseptic meningitis (Nigrovic et al. 2007; Sadarangani et al. 2015).

Neuroimaging in viral meningitis is typically normal although CT abnormalities including meningeal enhancement, hydrocephalus, ventriculomegaly and focal hypodensity have been reported in up to 12% of cases (Lee et al. 2006). MRI may demonstrate diffuse T1 enhancement of the meninges.

Management of Viral Meningitis

In the absence of specific treatments for the majority of viruses causing meningitis, supportive management is all that is required. A short period of hospitalisation for parenteral antibiotics is often considered appropriate while awaiting bacterial culture results. However, composite scoring systems, such as the Bacterial Meningitis Score, applied to a population of children with pleocytosis before bacterial culture results become available, are capable of identifying those at very low risk of bacterial meningitis with 99.9% accuracy (Nigrovic et al. 2007). If analgesia and hydration can be maintained orally such children may be safely managed at home with appropriate follow up, although this is not appropriate for young infants, the immunocompromised, or children pre-treated with antibiotics before lumbar puncture. Early detection of enterovirus in the CSF by rapid PCR is an alternative strategy for reducing hospitalisation, which may be employed more widely in future (Nigrovic et al. 2010).

There are no currently approved specific antiviral therapies for the enteroviruses, which comprise the bulk of viral meningitis cases (Abzug 2014). Headache duration in adults with aseptic meningitis was reduced by approximately two days in a randomised controlled trial of pleconaril, an antiviral agent with action against enteroviruses, although the benefit was relatively modest and restricted to patients with more severe disease (Desmond et al. 2006).

Outcomes of Viral Meningitis

The vast majority of patients with viral meningitis have a benign course and experience a complete recovery within 7–10 days. Communicating hydrocephalus occurs as a rare complication if the arachnoid granulations are obstructed by inflammatory debris. In the Canadian cohort 2% of 802 children required intensive care admission but there were no cases of coma or raised intracranial pressure and no deaths (Lee et al. 2006). Neonates may experience a higher rate of complications, especially if meningitis occurs as part of a disseminated viral infection affecting multiple organ systems.

Uncomplicated viral meningitis (i.e. without concomitant encephalitis) rarely results in long-term sequelae. Hearing loss may occur if infection spreads to the neighbouring structures of hearing. Viral meningitis occurring in the first three months of life may be associated with subsequent subtle delays in development of receptive language (Baker et al. 1996) but the long-term outcome is generally excellent. Chronic enteroviral meningoencephalitis is described in children with inherited or acquired antibody deficiencies (see Chronic Viral Infections section).

Viral Encephalitis

Encephalitis is a syndrome of neurological dysfunction caused by an inflammatory process involving the brain parenchyma. In most cases the meninges are also affected, and myelitis may also be part of the process; the terms meningoencephalitis and encephalomyelitis refer to a spectrum of pathology which includes encephalitis. Recent years have seen a number of advances in the diagnosis and management of encephalitis, including an expanded repertoire of molecular and imaging tests, a small number of novel antiviral therapies, and improved consensus on aciclovir treatment schedules for herpes simplex virus (HSV) encephalitis, the most common cause of devastating encephalitic disease.
Encephalitis is the most common form of acute non-suppurative neurological disease in childhood. The majority of cases are caused by viruses. Parasitic and bacterial causes of encephalitis are considered elsewhere in this chapter. Autoimmune encephalitides characterised by the presence of anti-neuronal autoantibodies are covered in Chapter 12. Acute encephalitides of viral origin can be subdivided into those directly related to viral invasion of the CNS (primary encephalitides) and those indirectly related (para- or post-infectious encephalitides), with the presence of detectable virus within the CNS supposed to differentiate the two. There also exists a separate category of acute encephalopathy syndromes occurring in association with viral infections and producing an ‘encephalitis-like’ illness in the absence of inflammation of the brain parenchyma. These syndromes are covered separately later in this chapter (see Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses section). In clinical practice, however, a pathological distinction between primary and post-infectious encephalitis, or even between encephalitis and para-infectious encephalopathies, is rarely possible as very few cases proceed to diagnostic brain biopsy.

Subacute and chronic encephalitides require a different approach to acute encephalitis, as the differential diagnosis in such cases includes neurodegenerative metabolic conditions and other slowly evolving disorders. Those viruses causing predominantly chronic encephalitides are covered separately later in this chapter (see Chronic Viral Infections section).

Epidemiology of Viral Encephalitis

Some viruses causing encephalitis are spread by human-to-human transmission only (e.g. herpes viruses, enteroviruses), others rely upon arthropod vectors for transmission (so-called arboviruses e.g. flaviviruses, alphaviruses), and a small number are transmitted from animals (e.g. henipaviruses, lymphocytic choriomeningitis virus). Incidence of the various causes of encephalitis varies significantly between countries; (due to e.g. restrictions in the range of arthropod vectors) and also within regions in a seasonal or epidemic pattern. Historically, public health measures have had an important impact on encephalitis epidemiology; vaccination against measles, mumps and rubella (MMR) substantially reduced the number of cases of encephalitis occurring in association with these agents (Koskineni and Vaheri 1989).

In Western settings the overall incidence of encephalitis in children is around 10.5–13.8 per 100,000 (Imor et al. 2008), or roughly five to seven patients per year in the average British district general hospital. HSV varicella zoster virus (VZV) and enteroviruses are the most commonly identified causes. Younger children and neonates are at higher risk. The largest prospective study of encephalitis epidemiology in the UK to date identified 203 cases (34% children) with encephalitis, defined as encephalopathy plus two or more of: fever, seizures and/or focal neurology, CSF pleocytosis, EEG suggestive of encephalitis, and neuroimaging suggestive of encephalitis (Granerod et al. 2010). The most common causes were HSV (19%), ADEM (11%), tuberculosis (5%), VZV (5%), anti-NMDA receptor antibodies (4%), anti-VGKC antibodies (3%), and streptococci (2%). Other viruses comprised a further 4% of cases; no cause was identified in 37%. The most recent report from the California Encephalitis Project found anti-NMDA receptor antibodies to be the most commonly identified cause of suspected encephalitis in children and young adults, seen in 4% of 761 cases, ahead of enterovirus (4%), HSV-1 (1%), VZV (1%), and West Nile virus (1%) (Gable et al. 2012). The high proportion of cases without an identifiable cause and low incidence of HSV encephalitis may be explained by a referral bias toward diagnostically challenging cases. The largest exclusively paediatric prospective epidemiological study to date was in Finland in the post-MMR era (Koskineni et al. 1997). Of 175 children presenting with suspected encephalitis, likely aetiological agents were identified in 63%; the most common were VZV (22%), respiratory viruses (20%), enteroviruses (19%), adenoviruses (5%), Epstein–Barr virus (EBV) (5%), HSV (5%) and rotaviruses (5%). Other recent European paediatric cohorts have found VZV (Vial et al. 2007) and HSV (Galanakis et al. 2009) to be the most common causes. Tick-borne encephalitis virus is an important agent in Slovenia (Cizman and Jazbec 1993) and some other parts of Eastern Europe. Other arboviruses are more important in Africa, Asia and the Americas (see Arboviruses section).

The UK Childhood Meningitis and Encephalitis Study (ChiMES) is an ongoing cohort study (UKCRN 14206) that should further expand our understanding of local epidemiology.
Clinical features of viral encephalitis

Some CNS viruses present with a characteristic set of signs and symptoms which are highly suggestive of the cause (e.g. rabies virus). These presentations are described in the organism-specific sections later in this chapter. However, most viral encephalitides present initially with a relatively nonspecific syndrome of which the core feature is encephalopathy, defined as altered mental status manifesting as reduced consciousness or altered cognition, personality or behaviour (Kneen et al. 2012). This usually appears acutely as confusion and drowsiness with variable deterioration in conscious level; in some cases a prodromal phase occurs with subacute onset of subtle memory and behavioural disturbances in the absence of frank obnubilation. Children with immunocompromise are more likely to present subacutely (Thompson et al. 2012). Other common clinical features include fever (67–80%), seizures (61–78%), focal neurological signs (37–78%) and vomiting (57%) (Kolski et al. 1998, Kneen et al. 2010). Older children may complain of severe headache. Seizures may be generalised or more subtle focal convulsions with, for example, twitching of the fingers or face (Solomon et al. 2007).

Encephalopathy may be preceded by a brief influenza-like illness; symptoms of respiratory or gastrointestinal infection are present in over half of children with confirmed encephalitis (Wang et al. 2007). Rashes may offer further clues to the cause; for example, hand, foot, and mouth disease (enterovirus), chickenpox (VZV), slapped cheek syndrome (parvovirus B19), and roseola (HHV-6) (Thompson et al. 2012). Of viral CNS infections in newborn infants, 85% are acquired vertically during delivery (Whitley 1994); features of primary viral infection may be present in the mother, for example, genital lesions of HSV. Focal neurological signs of encephalitis involve mostly the cerebral hemispheres (e.g. hemiparesis, dysphasia) but may also affect the brainstem and cerebellum, with ataxia present in 58% of cases in one encephalitis series (Rantala et al. 1991). Additional neurological manifestations include extrapyramidal signs (basal ganglia involvement), lethargy and sleep disturbance (hypothalamic involvement), and cranial nerve palsies and dysautonomia (brainstem involvement) (Lee et al. 2013).

Early recognition of symptoms suggestive of encephalitis is of vital importance as delayed initiation of treatment can impact negatively upon the outcome. Possible pitfalls include failure to take note of family reports of abnormal behaviour, finding false reassurance in the absence of fever, and incorrect attribution of confusion to other causes (fever, non-neurological infection, drugs, alcohol, psychiatric illness). Misdiagnosis of subtle or intermittent abnormal movements as manifestations of a nonspecific febrile illness must also be avoided. Clinical features of encephalitis in the neonate are often nonspecific and encephalopathy may be more difficult to detect in this age group.

Brainstem Encephalitis

Brainstem involvement is relatively common in encephalitis, especially in ADEM and the post-infectious encephalitides. It manifests as myoclonus, tremor, ataxia, autonomic dysfunction, respiratory drive disturbance and/or oculomotor and bulbar palsies (Lee et al. 2013). Isolated brainstem encephalitis is more unusual but occurs with a number of viruses including enteroviruses (especially EV-71), flaviviruses, alphaviruses and rabies virus (Kneen et al. 2012). The clinical presentation is of fever, systemic symptoms and aseptic meningitis, in association with symptoms and signs of brainstem dysfunction. Involvement of the oculomotor nerves and lower facial nerves is prominent and may be associated with obtundation and signs of involvement of the long tracts with resulting pyramidal and cerebellar manifestations. Cranial nerve involvement and ataxia may mimic the Fisher syndrome (see Chapter 22) that has been considered by some authors to be a form of brainstem encephalitis. Bacterial infections (listeriosis, brucellosis, Lyme disease), toxoplasmosis and tuberculosis also enter the differential diagnosis for primary encephalitis of the brainstem. Locked-in syndrome should be considered in cases of encephalitis with prominent brainstem involvement in which the degree of obtundation is out of proportion to cerebral involvement on neuroimaging and EEG.

Cerebellitis

Post-infectious cerebellitis is a well-recognised and usually self-limiting condition in children following viral infection, characterised by acute onset of cerebellar signs with or without meningeal, nausea, headache, altered consciousness and seizures (Kamate et al. 2009). Cerebellitis may also occur as a primary encephalitis caused by, for example, herpesviruses (particularly VZV and EBV), enteroviruses (Fig. 11.13), and mumps and measles in the unvaccinated (Amador et al. 2007). Rotavirus is also increasingly recognised as a cause of cerebellitis (see organism-specific section). The clinical course of viral cerebellitis is usually benign with complete recovery in the majority. A minority suffer fulminant cerebellitis (Kamate et al. 2009) which may require neurosurgical intervention (see Complications in the Viral Encephalitis section). Bacterial causes of cerebellitis include pertussis and diphtheria. Cerebellar lesions may also occur as part of CNS inflammatory demyelinating disease. Severe cerebellar atrophy with persistent cerebellar signs may follow the acute attack (Hayakawa and Katoh 1995).

Post-Infectious Encephalitis

Post-infectious or immune-mediated encephalitis presents with broadly similar features to primary encephalitis. In the majority of cases onset is abrupt with disturbances of consciousness and seizures. These symptoms appear on average six days (up to 21 days) after the occurrence of an upper respiratory tract infection or exanthematous infection, in most cases in a child over the age of 2 years. The range of neurological manifestations is as for any encephalitis, but a higher proportion of post-infectious encephalitides demonstrate extrapyramidal signs, and seizures are seen less frequently;
Table 11.8  Assessment and emergency management of the child with acute encephalopathy

**History**
Details of acute events: time of year; current local epidemics; prodromal illness; recent history of: infectious disease, travel, human contacts, animal contacts, insect contacts, fresh water swimming, drugs/toxins, recent immunisations
Past medical history: early development; seizures; consanguinity; family history; metabolic history; immune status; immunisation status; HIV risk factors

**General physical examination**
Airway, breathing, circulation (including blood pressure and peripheral perfusion status)
Skin and mucous membranes (exanthema, herpes)
Visceral examination
Lymphadenopathy
Animal and insect bites
Signs of drug misuse

**Neurological examination**
Level of consciousness using paediatric modifications of the Glasgow Coma Scale
Mini-mental state examination where possible (cognition and behaviour)
Ocular responses including corneal reflex, pupillary responses, oculocephalic reflex (doll’s eye manoeuvre), oculovestibular response
Motor asymmetry; response to noxious stimulation (appropriate withdrawal, decorticate or decerebrate posturing)
Signs of increased intracranial pressure especially examination of the fundi for papilloedema
Subtle motor seizures
Dyskinesia and other movement disorders
Meningism

**Laboratory investigations**
Blood gases, urea, electrolytes, creatinine, glucose
Full blood count and coagulation screen
Urinalysis for glucose and ketone bodies
Blood biochemistry: liver enzymes, ammonia, calcium
More complete metabolic investigations (lactic acid, amino acids, organic acids) in selected cases (preserve blood and CSF)
CSF – sugar (paired with blood), lactate and protein – unless clear contraindication to lumbar puncture (see Table 11.1)
Urine toxicology

**Microbiology**
Blood culture
CSF – MC&S x2, viral PCR panel (see text) +/- oligoclonal bands (if ADEM suspected) – unless clear contraindication to lumbar puncture (see Table 11.1)
Consider antibody testing of CSF and serum (see text)
If indicated by travel/contact history or clinical presentation:
- Mycobacterial culture and staining (Ziehl–Neelsen/auramine)
- Fungal culture and staining (India ink)
- Cytology to exclude malignant cells
- Rapid blood malaria antigen tests and three thick and thin films for malaria parasites
- Blood, urine, stool, throat, nasopharyngeal aspirate, skin lesions: culture/antigen testing/PCR for appropriate infections
- HIV status

**Immediate therapeutic measures**
Ensure adequate airway
Ensure safe intravenous access (using large veins if necessary)
immune-mediated encephalitis tends to favour involvement of white and deep grey matter over the cortex.

**Diagnosis of Encephalitis**

Encephalitis is a pathological diagnosis which can technically be made only on a tissue sample demonstrating inflammation of the brain parenchyma. As brain biopsy is rarely undertaken before other investigations have been exhausted, the diagnostic approach to suspected encephalitis in actual clinical practice is instead a process of narrowing the differential diagnosis of acute encephalopathy in a number of stages. Initial systematic assessment (see Table 11.8) is focused on identifying problems requiring immediate intervention and distinguishing meningoencephalitis from a range of other neurological, infectious, metabolic, vascular and toxic processes requiring alternative management. The most important diagnostic test for meningoencephalitis remains the lumbar puncture, which in the absence of contraindications should ideally take place prior to prompt commencement of empirical antimicrobial therapy. While the results of CSF analysis are awaited, neuroimaging and EEG should be arranged. Blood tests in viral encephalitis may reveal mild lymphocytosis but are otherwise useful only for exclusion of differentials, correction of electrolyte imbalance, and in some cases viral serology. Final diagnosis is guided by thorough review of the history, neurological examination, neuroimaging, EEG and laboratory studies, including results of molecular diagnostic testing.

**Differential diagnosis of encephalitis**

The differential diagnosis of encephalitis includes a large number of disorders marked by disturbances of consciousness arising from pathology inside and outside the CNS (Table 11.9). Because the clinical features are not specific, special attention...
## Table 11.9  Differential diagnosis of suspected encephalitis in a child

### Infections
- Bacterial or viral meningitis
- Septic encephalopathy
- Tuberculous meningitis
- Brain abscess
- Cerebral malaria

### Para- and post-infectious encephalopathies (see Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses section)
- Reye syndrome
- Haemorrhagic shock and encephalopathy
- Infantile bilateral striatal necrosis
- Acute necrotising encephalopathy
- Toxic shock syndrome

### Metabolic disorders
- Fluid, electrolyte and acid-base disorders
- Hashimoto’s encephalopathy
- Inherited metabolic disorders
  - Organic acidemias
  - Urea cycle disorders
  - Fatty acid oxidation disorders
  - Carnitine disorders
  - Respiratory chain defects

### Hypoxic–ischaemic injuries
- Vascular collapse and shock of various causes
- Cardiorespiratory arrest
- Near-miss sudden infant death syndrome

### Vascular diseases
- Cerebrovascular accident including thromboembolic and haemorrhagic stroke
- Vasculitis (systemic lupus erythematosus, Behçet’s disease, infectious and post-infectious causes)
- Venous thrombosis

### Toxic injuries
- Endogenous (diabetes, hepatic encephalopathy, renal encephalopathy)
- Exogenous (drugs or household agents, lead poisoning)

### Seizure disorders
- Status epilepticus
- Hemiconvulsions–hemiplegia syndrome

### Increased intracranial pressure
- Primary and metastatic brain neoplasia
- Subarachnoid and subdural haematoma
- Acute hydrocephalus

### Other
- Posterior reversible encephalopathy syndrome and hypertensive encephalopathy
- Aicardi-Goutières syndrome
- Lymphohistiocytosis syndrome
- Functional disorder
should be given to disorders that require immediate specific therapy, especially bacterial meningitis and encephalitis, tuberculous meningitis and brain abscess. Bacterial causes of encephalitis include *Mycoplasma pneumoniae*, rickettsiae, *Coxiella burnetii*, *Bartonella spp.*, *Brucella spp.*, *Listeria monocytogenes*, *Borrelia* and *treponema*. Exclusion of these may not be possible early in the course of the illness, even after results of initial CSF analysis and neuroimaging become available. Treatment with antibiotics and/or antituberculous agents may therefore be required in dubious cases, in parallel with treatment for HSV encephalitis, until the diagnosis is clarified.

Neuroimaging is required to exclude a wide range of non-infective differential diagnoses. Tumours, particularly those arising from the brainstem, may result in encephalopathy. Occasionally, an acute arterial thrombosis mimics an encephalitic process. Cerebral thrombophlebitis usually produces characteristic findings on neuroimaging. Both systemic vasculitis and primary CNS angiitis may also simulate viral encephalitis. Acute encephalitis may be fulminant but in many cases new symptoms and signs continue to appear over a few days to weeks. This is an important diagnostic feature, as in many other acute encephalopathies the full picture is abruptly completed.

Metabolic and toxic causes of encephalopathy must also be excluded. Intercurrent viral illness is a common precipitant of metabolic decompensation in children with unidentified underlying disease; therefore, the presence or absence of symptoms suggestive of a viral illness cannot be used to discriminate between metabolic encephalopathies and viral encephalitis. Features in the history which may point more toward a metabolic aetiology in the encephalopathic child include a more gradual onset, history of similar episodes in the past, and the absence of fever and pleocytosis. Features on examination favouring a metabolic over an encephalitic process include symmetrical neurological findings, myoclonus and clinical signs of liver failure. CSF pleocytosis and focal changes on MRI are usually absent in metabolic and toxic causes of encephalopathy (Kennedy 2004). Derangement of acid/base balance is a common feature of many metabolic disorders; capillary or venous blood gas analysis should be a routine part of the assessment of acute encephalopathy along with measurement of serum glucose, electrolytes and ammonia. In selected cases, amino acid and organic acid profiles should be obtained. In some patients examination of urine for toxic substances may be useful, although the course of intoxication is generally much faster and there are no focal neurological signs or meningeal involvement. Lead intoxication can mimic encephalitis; the CSF may show elevated protein but pleocytosis is absent and other features of lead toxicity are usually present. A subacute (weeks to months) history of encephalopathy should lead to consideration of autoimmune, paraneoplastic and metabolic causes.

As with any presentation, the differential diagnosis of suspected encephalitis should be informed by the previous medical history. Children with viral encephalitis are usually previously well. Recurrent episodes of febrile encephalopathy may suggest immunocompromise, *RANBP2* mutation (see Acute Necrotising Encephalopathy section) or Aicardi-Goutières syndrome. Children with a history of hypertension and/or immunosuppression are at increased risk of posterior reversible encephalopathy syndrome. Children with a history of cardiac or renal disease may be at increased risk of venous sinus thrombosis and other vascular events.

**LUMBAR PUNCTURE IN ENCEPHALITIS**

Lumbar puncture is essential in suspected encephalitis and failure to perform lumbar puncture is an important cause of missed diagnosis. All children with suspected encephalitis should have a lumbar puncture as soon as is safely possible following admission to hospital. Before embarking upon lumbar puncture, clinicians should review the contraindications listed in Table 11.1 and consider the accompanying advice regarding pre-lumbar puncture neuroimaging (see Clinical Manifestations and Diagnosis in the Acute Bacterial Meningitis in Infants and Children section). Lumbar puncture should not be delayed for neuroimaging unless there is a clear indication to do so, that is, clinical suspicion of raised intracranial pressure with brain shift. Such children may require further stabilisation prior to neuroimaging and any concerns should be discussed with an experienced anaesthetist. Known or suspected clotting abnormalities should be discussed with a haematologist prior to lumbar puncture.

Lumbar puncture for suspected encephalitis in children should include measurement of opening pressure (where possible), microscopy, culture and sensitivity studies, total and differential white cell count, red cell count, protein, lactate and glucose (paired with pre-lumbar puncture plasma glucose). Molecular (PCR) testing panel is determined according to local epidemiology and clinical presentation; in the UK, laboratories usually consider first-line testing for HSV-1, HSV-2, VZV, HHV-6, HHV-7, enteroviruses, parvo-viruses, adenovirus, influenza A and B and rotavirus (Solomon et al. 2007; Kneen et al. 2012). Other tests may be considered according to clinical presentation (e.g. with immunocompromise), including EBV, *cytomegalovirus* (CMV), measles, mumps, and parvovirus B19. Tests for arboviruses and other imported infections may be indicated by exposure and travel history. Additional CSF can be stored for further tests if required (e.g. antibody tests, see Molecular Diagnosis section) following discussion with the virologist or paediatric infectious disease specialist. Paired oligoclonal bands in CSF and serum should be examined if ADEM is part of the differential diagnosis.

The opening pressure is usually moderately raised in encephalitis. Laboratory analysis typically reveals abnormal CSF with a pleocytosis consisting of lymphocytes and mononuclear cells, a mildly elevated protein level and a normal glucose level. The CSF white cell count varies from a few to several hundred cells per cubic mm, in most cases with a majority of mononuclear cells, although polymorphonuclear cells may predominate in very acute cases with necrotic lesions, and in such cases red blood cells may also be present. CSF red cell count is elevated in approximately half of HSV encephalitis cases (Koskiniemi et al. 1984). Up to 10% of
patients with viral encephalitis have completely normal CSF cell counts and biochemistry, particularly early in the disease course, including some cases of proven HSV encephalitis (Whitley et al. 1989). VZV, EBV and CMV encephalitis are particularly associated with acellular CSF.

**Molecular diagnosis of encephalitis**

Isolation of specific nucleic acid in the CSF following PCR amplification is now the mainstay of diagnosis for viral infections of the CNS (Box 11.1). CSF PCR yield in suspected encephalitis is highest in the first week after disease onset (Koskinen et al. 2002) although false negatives occur in up to 29% of HSV encephalitis cases in the first 48–72 hours of illness (Tyler 2004; Whitley and Kimberlin 2005; To et al. 2014). In cases with a strong clinical suspicion of HSV encephalitis, in which the initial PCR is negative, it is useful to repeat the lumbar puncture 2–7 days later, even when aciclovir has been administered in the intervening period (Tunkel et al. 2008). PCR for HSV taken at day 2–10 of illness has greater than 95% sensitivity and specificity for HSV (Kneen et al. 2012). Recommendations for repeat PCR testing in established cases of HSV encephalitis at the end of treatment are discussed in Management in the Herpes Simplex Virus Encephalitis section.

Other techniques used for detection of virus in the CSF include culture, direct antigen detection, electron microscopy and antibody tests. These should be undertaken in close collaboration with specialists in microbiology, virology or infectious diseases. Antibody tests for consideration in suspected encephalitis include those against mycoplasma, chlamydophila, herpes viruses, enteroviruses, respiratory syncytial virus (RSV), parvovirus B19, adenovirus, influenza A and B, and (if travel history is suggestive) West Nile virus, tick-borne encephalitis, rabies virus and Japanese encephalitis (Kneen et al. 2012). Intrathecal antibody production to a specific virus provides strong evidence of the presence of a causative agent (Koskinen et al. 2002); CSF testing for HSV-specific IgG at 10–14 days of illness is particularly helpful in cases of suspected encephalitis where PCR of the CSF was not performed acutely (Kneen et al. 2012). Serological antibody positivity (demonstration of seroconversion or the presence of specific IgM) provides weaker evidence and must be interpreted in the context of background seroprevalence of the virus. Virus may also be detected in the throat, sputum, urine, rectum and any vesicles; viral isolation from these sites (especially vesicles) may be a helpful adjunct to diagnosis, but the results must be interpreted with caution.

In cases where a viral diagnosis remains elusive, testing for autoantibodies may be more cost effective than expanding the search for rarer viral agents, and more likely to result in the identification of a condition with specific treatment (i.e. immunomodulation) (Kirkham 2013; Weingarten et al. 2013). Even following autoantibody testing, 40% of suspected viral encephalitis cases remain without an identified aetiology. Brain biopsy has a diagnostic role after initial investigations have been exhausted in a small number of situations, including PCR-negative patients with suspected HSV encephalitis who deteriorate despite aciclovir (especially those with a focal lesion on imaging) (Pulhorn et al. 2008), patients with immunocompromise (Kneen et al. 2012), and patients with suspected vasculitis (Salvarani et al. 2007). One biopsy series of patients with presumed HSV encephalitis (conducted in the era before routine PCR testing) found HSV in 45%, other viruses in 9%, an alternative treatable disease in 9%, and an alternative non-treatable disease in 4% (Whitley et al. 1989).

**Neuroimaging in encephalitis**

Neuroimaging plays an important role in the diagnosis of encephalitis. MRI with diffusion-weighted imaging is the modality of choice for early identification of subtle changes, and is recommended within 24–48 hours of hospital admission in patients with suspected encephalitis in whom the diagnosis is uncertain (Kneen et al. 2012). Early CT is often normal in viral encephalitis and is used mainly as a rapid screening modality for alternative diagnoses and neurosurgical complications. Even with definitive MRI, in many cases the findings are nonspecific and must be interpreted together with the clinical history and laboratory investigations.

*Magnetic resonance imaging*

MRI is the most sensitive and specific imaging modality for viral encephalitis. Use of contrast is recommended as characteristic patterns of post-contrast enhancement may lead to identification of differential diagnoses (ADEM, suppurative abscess). The anatomical distribution of changes may in some cases be suggestive of the causative virus (Table 11.10) but there remains significant overlap among neurotropic viruses in appearance and location of changes on imaging. Of note, involvement of the cingulate gyrus and contralateral temporal lobe is highly suggestive of herpes encephalitis (Steiner et al. 2005). Imaging later in the disease course may show areas of haemorrhage. Further information on imaging findings in specific viral encephalitides is detailed in the organism-specific sections later in this chapter.

Input from an experienced neuroradiologist is invaluable in formulating the differential diagnosis of suspected viral encephalitis. Transient T2-hyperintensity and restricted diffusion of the cortical grey matter, subcortical white matter and hippocampi have been reported following status epilepticus in the absence of infection (Goyal et al. 2009; Chatzikostantinou et al. 2011); peri-ictal changes must therefore enter the radiological differential diagnosis in cases of suspected encephalitis with seizures, and repeat imaging may be helpful after seizures resolve. In encephalopathic patients with significant white matter lesions, ADEM should enter the differential diagnosis. ADEM presents with large, patchy, ill-defined lesions of T2- and FLAIR-hyperintensity in a predominantly subcortical and periventricular distribution, with various patterns of post-contrast enhancement (Rossi 2008).
Other modalities

CT is less sensitive than MRI for viral encephalitis and is often normal in early HSV encephalitis (Behzad-Bebahani et al. 2003). The principal advantages of CT are its availability and short scan time. It is therefore well suited to rapid screening for problems requiring urgent neurosurgical intervention, including several of the differential diagnoses listed in Table 11.9, in addition to acute complications of encephalitis such as hydrocephalus and brainstem compression. However, it is inappropriate as definitive imaging for encephalitis due to its very limited sensitivity. Exposure to ionising radiation is another factor limiting the use of CT in non-urgent situations.

Cranial ultrasound is a readily available bedside test in neonates with suspected brain infection. Cortical and subcortical oedema may be seen in encephalitis but sensitivity is poor, the depiction of brain convexity obtained is incomplete and posterior fossa abnormalities are poorly visualised (reviewed in Schneider 2011).

Functional and metabolic changes in encephalitis can also be investigated using MR spectroscopy, functional MRI (fMRI), single photon emission CT (SPECT), and positron emission tomography (PET). However, there is insufficient data to support the routine diagnostic use of these techniques in children with viral encephalitis at present (reviewed in Kneen et al. 2012).

Electroencephalography in Viral Encephalitis

EEG abnormalities are common in viral encephalitis, occurring in up to 75% of cases (Gable et al. 2012). The most common abnormality seen is nonspecific generalised or predominantly unilateral background slowing. These electrographic abnormalities may be apparent earlier than parenchymal change on MRI (Steiner et al. 2005), making EEG a useful investigation for demonstration of cerebral dysfunction early in the disease course in patients presenting only with subtle behavioural symptoms, in whom psychiatric and functional causes are in the differential diagnosis (Kneen et al. 2012). However, the severity of EEG abnormalities does not usually correlate with the extent of the disease and only rarely are specific features of the diagnosis identified. Periodic lateralised epileptiform discharges (Fig. 11.14) are often seen in HSV encephalitis, but also occur in other encephalitides (Hulihan et al. 1992; Garcia-Morales et al. 2002). EEG is also used for detection of subtle or nonconvulsive seizures or status epilepticus in encephalitis; use of continuous EEG monitoring identified seizure activity in 46% of 217 children enrolled in the California Encephalitis Project (Gold et al. 2014).

Management of Viral Encephalitis

Concerns regarding inconsistencies in the management of suspected encephalitis in children (Kneen et al. 2010), including indications for starting aciclovir and appropriate duration of treatment once started, led to the formulation of national guidelines by the Association of British Neurologists and British Paediatric Allergy Immunology and Infection Group (Kneen et al. 2012). The recommendations of the group are referred to throughout this section. The initial assessment and stabilisation of children with suspected encephalitis is the same as that of other acute encephalopathies and is a paediatric emergency. Priority must be given to ensuring a patent airway and maintaining adequate circulation. A complete assessment of the child is then in order (see Table 11.8). Neurological examination is essential in establishing the correct diagnosis, evaluating prognosis and planning therapy. When a diagnosis cannot be established or a patient fails to improve with therapy, transfer to a paediatric neurological unit is recommended. Children with suspected infective encephalitis should be notified to the regional Consultant in Communicable Disease Control.

Table 11.10 Known neuroanatomic tropisms of specific acute viral agents

<table>
<thead>
<tr>
<th>Tropism</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia and thalami</td>
<td>Flaviviruses, respiratory viruses, HHV-6, alphaviruses, EBV, VZV, mumps, enteroviruses, rotavirus</td>
</tr>
<tr>
<td>Anterior horns of the spinal cord</td>
<td>WNV, poliovirus, coxsackieviruses, EV71</td>
</tr>
<tr>
<td>Frontal lobes</td>
<td>HSV-1, HHV-6, CMV</td>
</tr>
<tr>
<td>Parietal lobes</td>
<td>HSV-1, CMV</td>
</tr>
<tr>
<td>Hippocampi and limbic system</td>
<td>HSV-1, HHV-6, EBV, rabies virus</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>HSV-1, HHV-6, WNV</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Enteroviruses (esp. EV71), parechoviruses, flaviviruses, alphaviruses, rabies virus, HHV-6, EBV</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>VZV, rotavirus, EBV, HHV-6, coxsackieviruses, parechoviruses, WNV, TBEV, JE</td>
</tr>
<tr>
<td>Ventriculitis</td>
<td>CMV, VZV, HIV</td>
</tr>
<tr>
<td>Splenium of the corpus callosum</td>
<td>Influenza A and B, mumps, adenovirus, rotavirus, EBV</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>JCV, paramyxoviruses, HSV, parechoviruses, rotavirus, parvovirus</td>
</tr>
</tbody>
</table>

*References are in organism-specific sections.

EBV, Epstein–Barr virus; VZV, varicella zoster virus; EV71, enterovirus 71; HSV, herpes simplex virus; HHV, human herpes virus; CMV, cytomegalovirus; HHV-6, WNV, West Nile virus; TBEV, tick-borne encephalitis virus; JE, Japanese encephalitis; HIV, human immunodeficiency virus; JCV, John Cunningham virus.
**Antimicrobial therapy**

The antimicrobial treatment of CNS viral infections remains limited. The main drugs active against viruses are shown in Table 11.11. Randomised controlled trials in adults showed administration of aciclovir reduced mortality in HSV encephalitis from 42–67% to less than 25% (Whitley et al. 1986). As HSV is the most common cause of devastating viral encephalitis in children it is accepted practice to administer intravenous aciclovir in suspected viral encephalitis prior to PCR confirmation of HSV. The dose of aciclovir is 500mg/m² intravenously 8 hourly (ages 3 months to 12 years) or 10mg/kg 8 hourly (ages over 12 years), with smaller doses in children with renal impairment (Kneen et al. 2012). Please refer to the Paediatric British National Formulary, or local guidelines, for further details on preparation or dosage. Adequate hydration should be maintained and renal function monitored while giving intravenous aciclovir as reversible nephropathy occurs in up to 20% of patients after several days of treatment (Pacheco et al. 2005).

Aiclovir should be started within 6 hours of admission in any case in which acute viral encephalitis is suspected (Kneen et al. 2012). If there are no contraindications to immediate lumbar puncture (Table 11.1) this should precede initiation of aciclovir. Treatment may be withheld pending initial CSF and neuroimaging results in relatively well children with a lower pretest suspicion of HSV encephalitis (i.e. those with a subacute to chronic history, mild encephalopathy only, absence of fever, and/or signs and symptoms suggestive of an alternative diagnosis). In cases where immediate lumbar puncture is contraindicated, aciclovir therapy should be given prior to lumbar puncture if the anticipated delay in arranging and interpreting urgent neuroimaging is greater than six hours, or if the child is clinically unwell or deteriorating. If bacterial sepsis, meningitis, encephalitis or cerebral abscess are suspected, broad spectrum antibiotics should also be given. The only other empirical antiviral treatment which might be considered in previously well UK children with negative contact and travel history is oseltamivir in flu season (Thompson et al. 2012). Treatment of established (i.e. PCR proven) viral encephalitis is discussed in the relevant organism-specific sections later in this chapter.

If any bacterial or tropical cause of encephalitis is suspected, treatment should be discussed with an expert in infectious diseases, virology or microbiology. It is reasonable to start empirical antimalarial treatment in encephalopathic children returning from malarial areas, in whom cerebral malaria is suspected, if delays in obtaining results of laboratory tests for malaria are anticipated (WHO 2010a).

**Decision to stop aciclovir**

A common clinical dilemma occurs when a patient presenting with febrile encephalitis and treated initially with aciclovir is found to have a negative CSF PCR for HSV. Once started, can aciclovir be stopped early, especially as three weeks of intravenous treatment is quite onerous in small children? Caution is required as false negative results are not uncommon in CSF samples taken in the first 72 hours of illness (Tyler 2004; Whitley and Kimberlin 2005; To et al. 2014). Aiclovir can be stopped in an immunocompetent child if there is no ongoing clinical suspicion of HSV encephalitis; i.e. if an alternative diagnosis has been made, or a negative PCR has been obtained at more than 72 hours post onset.
of neurological symptoms in a recovered child with normal neuroimaging, normal CSF white cell count and normal conscious level (Thompson et al. 2012). A still more cautious approach might include normal EEG and normal neuroimaging at more than 96 hours post onset of neurological symptoms in these criteria. A repeat lumbar puncture should be undertaken in patients with an ongoing clinical suspicion of HSV encephalitis if the first was taken at less than 72 hours post onset of neurological symptoms; HSV encephalitis is very unlikely if two CSF samples obtained 24–48 hours apart are PCR negative (Kneen et al. 2012). Treatment should otherwise be continued for at least 10 days. If HSV encephalitis is strongly suspected; for example, if imaging or EEG demonstrates a focal abnormality, then a full 21 days of aciclovir should be completed.

**Immunomodulation**

Adjunctive corticosteroid therapy has been tried in HSV encephalitis to reduce deleterious neuroinflammation, but the risks of immunosuppression in active infection may be significant; evidence is not yet sufficient to recommend this as standard practice (Ramos-Esteban et al. 2014). However, children with neuroimaging and other features supporting a diagnosis of ADEM over viral encephalitis should be treated with steroids as first-line treatment (see Chapter 12). Children with antibody-mediated encephalitis often require steroids and other immunomodulatory treatments (see Chapter 12). Steroids may be tried in cerebellitis if symptoms are severe. Future treatments for viral encephalitis may incorporate targeted blocks of interleukin-1 and other pro-inflammatory mediators.

**Supportive care**

Children with encephalitis should be monitored closely on a neurological ward or high dependency unit. Critically ill children with a very depressed or falling level of consciousness are best treated in intensive care units and this applies particularly to those with signs of raised ICP. Maintenance of an adequate cardiac output to support effective cerebral perfusion is essential, alongside close monitoring of respiration, blood pressure and body temperature to maintain homeostasis. Nasogastric or parenteral feeding may be required. Electrolyte imbalances are common and should be carefully monitored and corrected. Hyperthermia and seizures must be kept under control as far as possible; uncontrolled seizures lead to increased metabolic activity, acidosis and intracranial vasodilatation, exacerbating risk of raised intracranial pressure (Solomon et al. 2007). Continuous EEG monitoring is extremely useful in detecting subclinical seizure activity and evaluating the degree of brain...
Continuous ICP monitoring led to changes in the clinical management (anticonvulsant initiation/escalation/discontinuation; urgent neuroimaging) in 59% of cases (Abend et al. 2011). Continuous ICP monitoring is not generally required in acute encephalitis but may be required in some related conditions such as Reye syndrome (see Reye Syndrome section).

Rehabilitation
Consideration of physical, psychological and educational rehabilitation should begin during convalescence (Thompson et al. 2012). Multidisciplinary input from occupational therapy, speech and language therapy, physiotherapy, neuropsychology, child psychiatry and other teams may be required. Spasticity, dystonia and epilepsy may require pharmacological management. Referral to specialist brain injury rehabilitation services should be considered for complex or severe cases. Up to 96% of families report ongoing symptoms at discharge (Easton et al. 2007); details of voluntary sector organisations should be provided to parents, and outpatient followup should be offered. Referral to community paediatrics may be required for developmental follow-up.

Complications of Viral Encephalitis

Neurosurgical complications
Raised ICP can occur in viral encephalitis as a consequence of brainstem involvement and/or cerebral oedema. Management of raised intracranial pressure is discussed in Chapter 7; measures such as 30 degree head-up positioning, maintenance of low-normal pCO2, osmotic agents and corticosteroids may be required (Solomon et al. 2007). Decompressive craniectomy may be considered in encephalitis patients with clinical and imaging evidence of brainstem compression. Adult case series suggest surgical management of brainstem compression may be superior to medical management alone (Perez-Bovet et al. 2012). Excellent recovery of neurological function is possible in some cases (Adamo and Deshaies 2008).

Fulminant cerebellitis may cause marked swelling of the cerebellum with obstructive hydrocephalus requiring external ventricular drainage or even posterior fossa decompression (Amarador et al. 2007). The course may be fatal, particularly when associated with brainstem compression or transtorial and/or transforminal herniation (Levy et al. 2001; Gamanagatti and Nayaz 2008).

Status epilepticus
Status epilepticus is reported in 15% of encephalitis cases of all ages and aetiologies (Solomon et al. 2002) and is probably more common in the paediatric group. Management of status epilepticus is discussed in Chapter 16. In the California Encephalitis Project, 4% of cases (including adults and non-infective aetiologies) suffered treatment-refractory status epilepticus which required induction of anaesthetic coma to terminate; the risk was higher in children, those with infectious symptoms, and those with normal initial neuroimaging (Glaser et al. 2008). Nonconvulsive status epilepticus should be considered as a cause of persisting encephalopathy in viral encephalitis.

Other complications
Lacunar infarcts in the central grey matter or internal capsule may result from vascular occlusion or focal cerebritis. Some viruses (e.g. VZV) are associated with vasculitis; magnetic resonance angiography should be performed if vasculitis is suspected (Nagel et al. 2008). The syndrome of inappropriate antidiuretic hormone (SIADH) is common in encephalitis (Solomon et al. 2007) and diabetes insipidus may also occur (Steiner et al. 2005). Patients with encephalitis are at risk of developing aspiration pneumonia. Postencephalitic parkinsonism is unusual in children but is associated with some flaviviruses (Solomon et al. 2007).

Outcome of Viral Encephalitis
In UK children, 2–3% of viral encephalitis cases are fatal (Davison et al. 2003). Mortality is associated with younger age and particularly with HSV encephalitis. Post-infectious encephalitis usually runs a more benign course, with low mortality, and recovery in less than two weeks in three-quarters of cases.

Survivors of encephalitis often suffer physical, cognitive, emotional, behavioural, and social difficulties following the acute illness (Clarke et al. 2006). Outcome of viral encephalitis in children has not been extensively studied; some known prognostic factors for neurological outcome in children and adults with encephalitis are listed in Table 11.12.

Table 11.12 Prognostic features in viral encephalitis

<table>
<thead>
<tr>
<th>Positive prognostic features</th>
<th>Negative prognostic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS &gt;10 at onset of therapy</td>
<td>Younger age (Ito et al. 1998; Lahat et al. 1999; Whitley and Kimberlin 2005; Ward et al. 2012)</td>
</tr>
<tr>
<td>Early administration of aciclovir</td>
<td>Focal neurological signs at presentation (Fowler et al. 2008)</td>
</tr>
<tr>
<td>Rapid improvement in EEG</td>
<td>Status epilepticus unresponsive to standard antiepileptic therapy (Glaser et al. 2008)</td>
</tr>
<tr>
<td>CSF pleocytosis (Fowler et al. 2008)</td>
<td>Status epilepticus during acute illness (Herrmann et al. 2006)</td>
</tr>
</tbody>
</table>

Studies referring specifically to herpes simplex virus encephalitis. GCS, Glasgow Coma Scale.
Of children with HSV encephalitis, 63–79% suffer long-term sequelae including developmental delay, motor deficits, neuropsychiatric problems and seizures (Ito et al. 1998; Elbers et al. 2007; Ward et al. 2012). Neuropsychiatric problems in viral encephalitis include anxiety, depression, obsessive behaviours, hyperactivity/concentration difficulties and memory problems (Kneen et al. 2012). Outcome in encephalitis with an identified causative agent is detailed in the organism-specific sections later in this chapter. Even children with apparently favourable initial outcome may be at risk of developing problems in later life; research suggests exposure to CNS infection and neuroinflammation in early life leads to altered immunological phenotypes with increased susceptibility to secondary CNS insults and increased risk for a range of disorders including cerebral palsy, epilepsy, autism, multiple sclerosis, schizophrenia and adult-onset neurological diseases (Hagberg et al. 2012).

**ACUTE ENCEPHALOPATHY SYNDROMES OCCurring IN ASSOCIATION WITH VIRAL ILLNESSES**

Several specific syndromes of CNS disease are described, which occur in close temporal relationship to a defined or undetermined viral infection, in the absence of direct viral invasion of the CNS. These acute para-infectious encephalopathies (see Table 11.13) present as secondary deteriorations in consciousness in the context of a viral illness. Seizures and vomiting commonly accompany the encephalopathy, which can range from mild to profound. The extent to which these syndromes represent a spectrum of related conditions is not yet clear; the pathological mechanisms are heterogeneous and poorly understood, although in several syndromes pathogenesis is related to abnormal host cytokine response (cytokine storm) and culminates in a final common pathway of malignant brain oedema. Neuroinflammation may play a role in some of these syndromes but is not widespread and fulminating as in acute disseminated encephalomyelitis. Although a range of viruses may cause these presentations, influenza A and B (and to a lesser extent HHV-6 and HHV-7) are particularly common triggers. Genetic differences in host response may explain the increased incidence of several of these syndromes in Asian children.

Further to the syndromes listed in Table 11.13 and outlined in greater detail below, there are a number of other causes of encephalopathy in the context of viral illness which should be considered in the differential diagnosis. Acute decompen-sation of a pre-existing mitochondrial or other metabolic abnormality (see Table 11.14) may be triggered by intercurrent viral infection; serum ammonia, serum amino acids and urine organic acids are recommended in any child with severe encephalopathy of unclear aetiology. These investigations should be normal in the conditions listed in Table 11.13, with the exception of Reye syndrome, which may be associated with hyperammonaemia. Some encephalopathies may be caused by status epilepticus or its complications (e.g. aspiration). Others may be the consequence of shock or circulatory failure occurring as part of a severe viral infection (Kirkham 2013). Raised ICP must be considered in any acute presentation of encephalopathy. Derangements of fluid and electrolyte balance may occur in viral illness; hyponatraemia is a common finding in clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) (Takanashi 2009). Posterior reversible encephalopathy syndrome is sometimes associated with influenza infection. Viruses leading to acute anaemia and hypoxia in children with pre-existing haemoglobinopathies may also cause encephalopathy (Wierenga et al. 2001).

**Reye Syndrome**

Reye syndrome is a rare, severe, acute, noninflammatory encephalopathy occurring in association with hepatic dysfunction. Most cases are associated with antecedent viral illness (Singh et al. 2011). Occurrence is closely linked to ingestion of aspirin during the antecedent illness (Starko et al. 1980; Glasgow 2006). The pathogenesis remains unclear and may comprise a group of heterogeneous disorders (Casteels-Van Daele et al. 2000). Pathologically the disease is characterised by microvesicular fatty degeneration of the liver and sometimes kidneys (Devivo and Keating 1976) with or without brain oedema. Multiple causes have been identified but in most cases there is a clear association with a viral illness. Implicated agents include varicella (Hurwitz et al. 1982), influenza A (Starko et al. 1980), influenza B (Norman 1968), adenovirus and cytomegalovirus (Qi et al. 2013). The association of Reye syndrome with administration of aspirin was first suggested by epidemiological studies and later confirmed as a dose-dependent effect of aspirin administration in children with viral infection (Starko et al. 1980). Following subsequent advice to avoid salicylate use in febrile children there was a dramatic decrease in incidence in the 1980s (Bhatta et al. 2003). Most hypothesised mechanisms are based on the presence of biochemical and pathological changes suggestive of generalised mitochondrial dysfunction. Direct mitochondrial involvement by a virus is conceivable but no virus has ever been isolated from the liver or brain. Another possibility would be the decompensation of a latent innate metabolic abnormality precipitated by viral infection and/or cofactors such as aspirin; in vitro studies show the drug acts on the mitochondrial long-chain hydroxyacyl-CoA dehydrogenase enzyme (Glasgow 2006).

**Clinical Features of Reye Syndrome**

The clinical manifestations of Reye syndrome appear after the symptoms of the premonitory disease have subsided and in the absence of fever. Initial symptoms include repeated vomiting with progressive deterioration of consciousness to stupor and coma in severe cases (Ozdoba et al. 1997). Convulsions may occur and changes in muscle tone in the form of opisthotonus.
Central neurogenic hyperventilation can be seen in the later stages. The liver is enlarged in about half of cases. The clinical picture is conspicuous for the absence of focal neurological signs and absence of icterus. Clinical manifestations of raised ICP may be prominent, including papilloedema and signs such as mydriasis and decerebrate attitude that indicate brainstem dysfunction. Elevated liver enzymes (aspartate transaminase and alanine transaminase) are an early feature. Bilirubin rarely rises above 50mmol/L. Hyperammonaemia is typical but may be transient and occurs relatively late in the course of the illness. Hypoglycaemia is present in about half of cases and is more common in infants. Prolonged prothrombin time and elevated creatine kinase are sometimes observed. CSF is under high pressure but laboratory analysis is normal. MRI may show T2-weighted abnormalities in the thalamus, midbrain and pons, with or without diffuse brain oedema (Ozdoba et al. 1997; Singh et al. 2011). As the oedema is usually cytotoxic, restricted diffusion may be observed. Watershed involvement in the subcortical white matter and parasagittal cortex may reflect hypoperfusion injury (Singh et al. 2011). As Reye syndrome is now very rare, any infant or child suspected of having the disorder should undergo extensive investigation to rule out inborn metabolic disorders that may mimic it (see Table 11.14).

### MANAGEMENT AND OUTCOME OF REYE SYNDROME

The management of Reye syndrome is supportive. Careful attention to metabolic and physiological disturbances including hypoglycaemia, hypoxia-ischaemia, electrolyte imbalance and bleeding diathesis may suffice in many early cases. In more severe cases, an aggressive therapeutic approach seems justified given the high mortality rate. Intensive care, mechanical ventilation, correction of metabolic abnormalities as well as monitoring and treatment of intracranial hypertension are essential. Mortality in children was 50–60% in the early 1970s but has now improved with earlier recognition and superior supportive care. Mortality is
highest in children under 5 years of age and in those with a serum ammonia level above 45µg/dL (26µmol/L) (Belay et al. 1999).

**Acute Infantile Bilateral Striatal Necrosis**

Acute infantile bilateral striatal necrosis (IBSN) is a rare neurological syndrome occurring following a nonspecific febrile illness in infants. The aetiology of the syndrome remains unclear. Implicated organisms include *M. pneumoniae* (Larsen and Crisp 1996), echovirus 25 (Peters et al. 1979), mumps (Goutières and Aicardi 1982), measles (Cambonie et al. 2000) and others (Zevit et al. 2007). Acute IBSN is differentiated from these by its acute onset, temporal relationship to a triggering infective event, and non-progressive, typically more benign course. The differential diagnosis includes acute bilateral infarction of the striatum, which may occur following trauma or spontaneously (Bogousslavsky et al. 1988), but lacks the inflammatory features of IBSN.

**Management and outcome of IBSN**

Favourable response to corticosteroid therapy has been reported (Yamamoto et al. 1997), although even without treatment the natural course is of resolution over weeks to months without recurrence. However, extrapyramidal sequelae occur in most cases (Goutières and Aicardi 1982; Rosemberg et al. 1992) with persisting striatal lesions up to 5 years after the acute insult (Roig et al. 1990). Behavioural problems and learning difficulties may also occur, although milder cases with full recovery are described (Kim et al. 1995).
Haemorrhagic Shock and Encephalopathy Syndrome

Haemorrhagic shock and encephalopathy syndrome (HSES) was first described in 1983 (Levin et al. 1983). The alternative term acute shock with encephalopathy and multi-organ failure (ASEM) has been proposed (Goenka et al. 2014). The pathogenesis of this devastating disease remains unclear but onset is associated with viral infection in most cases; viruses isolated from peripheral sites include influenza, human herpes virus 6, norovirus, adenovirus, rotavirus and bocavirus (Gefen et al. 2008; Goenka et al. 2014; Kuki et al. 2015). Hyperpyrexia, hypoxia, oxidative injury, aberrant cytokine response, defective synthesis/reuptake of protease inhibitors and acute dysfunction of the cerebral perfusion regulatory system have been proposed as pathophysiological mechanisms (Jardine and Bratton 1995; Gefen et al. 2008; Kuki et al. 2015).

Clinical features of HSES

The median age at onset is 15 months (Kuki et al. 2015). Presentation is typically with acute onset of watery diarrhoea (Gefen et al. 2008) followed rapidly by shock and encephalopathy with unresponsiveness and seizures. Fever of 39.5°C or higher is typical. Profound hypotension leads to skin mottling and other signs of hypoperfusion. Oozing of blood occurs at puncture sites due to disseminated intravascular coagulopathy. Multi-organ failure with hepatic and renal involvement follows. Diagnosis is based on clinical criteria (Levin et al. 1989): shock, convulsive coma, fever and oliguria are mandatory features; diarrhoea and haemorrhage are supportive. The CSF is normal. The characteristic imaging finding is of widespread ischaemia affecting the watershed zones of the cortex with sparing of the thalamus and brainstem. CT is usually normal in the first 24 hours but subsequently shows loss of grey/white differentiation and watershed hypodensity with progression to widespread brain oedema. MRI shows swollen, T2-intense cerebral cortex and ischaemic changes in watershed zones. Diffusion-weighted MRI may detect cytotoxic oedema early in the disease course. The overall picture has been compared to changes seen in shaken baby syndrome (but without subdural haematoma) (Kuki et al. 2015). The EEG shows early focal or multifocal spikes with diffuse slowing (Tsai and Baker 2013). An extensive search for infective causes is required as the differential diagnosis includes haemolytic uraemic syndrome secondary to *E. coli* O157:H7, Eikiri syndrome secondary to *Shigella*, staphylococcal toxic shock syndrome and viral haemorrhagic fever (Ebola, Lassa, Marburg) (Gefen et al. 2008; Kuki et al. 2015).

Management and outcome of HSES

Treatment is supportive and often requires an intensive care setting for fluid replacement, vasopressors, intracranial pressure depressants and mechanical ventilation. There is no proven specific therapy although many patients are treated with steroids. Plasmapheresis (Roth et al. 1987) and therapeutic hypothermia (Kuki et al. 2015) have also been tried. Recovery from multi-organ failure can be relatively rapid but the acute illness is fatal in 37–60% of patients and neurological sequelae are present in 30–100% of survivors (Thebaud et al. 1999; Kuki et al. 2015). Absence of disseminated intravascular coagulation is associated with better prognosis. Poorer prognosis is associated with biphasic course, status epilepticus, longer duration of coma, and loss of grey/white differentiation on CT (Gefen et al. 2008; Kuki et al. 2015).

Acute Necrotising Encephalopathy

Acute necrotising encephalopathy (ANE) is a rare, severe and often fatal condition, also termed symmetrical thalamic necrosis (Yagishita et al. 1995; Mizuguchi 1997). It is triggered by a range of viral infections, particularly influenza A (Grose 2004; Tsai and Baker 2013) but also influenza B (Youdris et al. 2001; Grose 2004; Huang et al. 2004b), parainfluenza, human herpes virus 6 (Oki et al. 1995), mumps (Watanabe et al. 2013), varicella zoster virus, rotavirus (Hoshino et al. 2012) and nonviral triggers including *M. pneumoniae* and vaccinations (Neilson 2010). Host predisposition to an aberrant inflammatory response is proposed to be the main pathophysiological mechanism and susceptibility is partly genetically conferred; the condition occurs more often in Japanese children, and a familial form (ANE1) is caused by missense mutations in the *RANBP2* gene (Neilson et al. 2009; Goenka et al. 2014; Singh et al. 2015). Younger children are more susceptible.

Clinical features of ANE

The clinical presentation is with fulminant encephalopathy and coma occurring 1–5 days following onset of a febrile illness. Polyfocal neurological signs are typically accompanied by seizures, which may be treatment-refractory (Tsai and Baker 2013). CSF commonly shows elevated protein (Goenka et al. 2014) and may show mild pleocytosis (Tsai and Baker 2013). Hepatic involvement ranges from elevated serum transaminases to overt liver failure. Neuroimaging reveals symmetrical, multifocal lesions affecting primarily the bilateral thalamus and brainstem, appearing as hypodensity on CT and T2-hyperintensity on MRI (Wong et al. 2006) (Fig. 11.16). Diffusion imaging reveals lamellar thalamic change with vasogenic oedema on the outside and cytotoxic oedema reflecting haemorrhage and necrosis on the inside (Albayram et al. 2004). Other areas of involvement may include the cerebellum, hippocampus, putamen, internal and external capsule, medial temporal lobes and periventricular white matter (Kneen et al. 2012); cases may initially be misdiagnosed as acute disseminated encephalomyelitis (Singh et al. 2015). The differential diagnosis also includes arboviruses and rabies (Tsai and Baker 2013).

Management and outcome of ANE

Prompt treatment with steroids is recommended; administration in the first 24 hours of illness is associated with better outcome (Okumura et al. 2009). Further immunomodulation may be required for recurrent encephalopathy in those with *RANBP2* mutations (Singh et al. 2015). Around one-third of
cases are fatal and another third are left with severe cognitive and motor impairment (Okumura et al. 2009). Prognosis is poorer in those with pontine involvement (Kneen et al. 2012) or haemorrhagic/cavitating lesions (Wong et al. 2006) on neuroimaging. However, full recovery has been reported, including in some children who did not receive steroid treatment (Loh and Appleton 2010).

**Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion**

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a recently described syndrome (Takanashi et al. 2006) associated with various viral infections including influenza A and B, HHV-6, HHV-7 and rotavirus (Takanashi et al. 2009; Hoshino et al. 2012). Theophylline may also be a trigger. There is probably overlap with a previously described syndrome termed acute infantile encephalopathy predominantly affecting the frontal lobes (Yamanouchi and Mizuguchi 2006; Goenka et al. 2014). Cases described to date have mostly been in Asian children. Magnetic resonance spectroscopic findings of decreased N-acetylaspartate and elevated glutamine/glutamate complex suggest excitotoxic neuronal damage as a possible pathogenic mechanism (Takanashi et al. 2009).

The syndrome is characterised by a prolonged (>30 minutes) febrile seizure as the initial neurological symptom, followed by a seizure-free interlude in which the patient may be encephalopathic or apparently symptom free. Seizures return on days 4–6, occurring as clusters of complex partial seizures with secondary generalisation with or without fever (Tsai and Baker 2013), accompanied by deterioration in consciousness. As seizures resolve frontal lobe dysfunction (e.g. speech regression) and stereotyped movements predominate. CSF shows normal white cell count and protein. Serum aminotransferase may be elevated but ammonia level is normal. EEG is acutely abnormal with slowing and/or epileptic discharges. Early MRI is normal. Diffusion-weighted imaging on days 3–9 reveals subcortical hyperintense lesions, evolving into cortical hyperintensity later in the disease course, with mostly symmetrical lesion distribution in the frontal and fronto-parietal regions (Takanashi 2009).

Management is symptomatic; immunomodulation and therapeutic hypothermia have been tried but there is no evidence for efficacy. Mortality is less than 5% (Mizuguchi et al. 2007) but sequelae including cognitive impairment, epilepsy and cerebral atrophy are common. However, the clinical spectrum is wide and many children have a milder course with full recovery.

**Clinically Mild Encephalitis/Encephalopathy with Reversible Splenial Lesion**

Clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is another relatively recently described syndrome (Tada et al. 2004; Takanashi 2009; Takanashi et al. 2009) associated with viral infections including influenza A and B (Ganapathy et al. 2008; Tsai and Baker 2013), mumps, adenovirus and rotavirus. Cases following infection with streptococci and *E. coli* have also been reported. The pathogenesis is not clear but may relate to focal cerebral oedema secondary to electrolyte/fluid imbalance or inflammatory infiltration.

The history is of a prodromal febrile illness followed 1–3 days later by encephalopathy characterised by delirium, abnormal behaviour and/or seizures. CSF may show pleocytosis (Tsai and Baker 2013). Hyponatraemia is a typical finding (mean 131.8 mmol/L). EEG shows diffuse slow waves in around half

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**Figure 11.16** T2-weighted axial fluid attenuated inversion recovery images in a 3-year-old boy showing high signal in external capsules (a) bilaterally and (b) in left cerebellar grey matter. (Courtesy of Dr E Wassmer, Birmingham Children’s Hospital, UK.)
MRI reveals T2 hyperintensity with restricted diffusion in the corpus callosum in all cases, mostly limited to the splenium. Around one-fifth of cases have involvement of nearby white matter bilaterally (Takanashi 2009).

Patients are often treated with steroids but the natural course is of complete recovery and resolution of neuroimaging abnormalities within one month (Ganapathy et al. 2008; Takanashi 2009).

## ACUTE VIRAL AGENTS

### HUMAN HERPES VIRUSES

Viruses of the family *Herpesviridae* cause a range of CNS infections and are the most common cause of encephalitis in children. The name ‘herpes’ is derived from the Greek *herpein*, meaning ‘to creep’, reflecting the insidious character of this ubiquitous family of neurotropic viruses, which are capable of causing lifelong latent infection in the host and reactivating in later life. Reactivation sometimes occurs during a period of relative immunosuppression, and may occur many years after primary infection, which is usually mild and self-limiting.

Of some 130 herpesviruses, six are well known as agents of CNS infection in humans (see Table 11.15); human herpes virus 7 (HHV-7) has less frequently been associated with CNS infection but is also included. All herpesviruses have large double-stranded DNA genomes which are transcribed to mRNA within the host cell’s nucleus. During acute infection, transcription of lytic genes leads to viral replication. During latency, different viral genes are expressed leading to persistence of virus in the host cell, potentially indefinitely, or until reactivation leads to transcription of lytic genes once more.

The alpha-herpesviruses (HSV-1, HSV-2, VZV) have relatively short replication cycles and tend to infect and destroy a broad range of host cells, establishing latent infection in the sensory ganglia. The gamma-herpesvirus EBV is specific for B lymphocytes and remains latent in lymphoid tissue. The beta-herpesviruses (CMV, HHV-6, HHV-7) have relatively long replication cycles, tend to cause enlargement of affected cells, and establish latency in secretory glands and lymphoreticular cells.

### Herpes Simplex Virus

HSV is one of the most common (Galanakis et al. 2009; Granerod et al. 2010) and most devastating causes of encephalitis in Western countries. One population-based study found HSV infection of the CNS accounted for 23% of all serious neurological infections in children aged 2–11 months and 4.5% in older children (Ward et al. 2012). HSV comprises serotypes HSV-1 and HSV-2. In this section four presentations are considered in turn: HSV encephalitis in children and adolescents, which is usually caused by reactivation of HSV-1; HSV meningitis in children and adolescents, which is usually caused by HSV-2; perinatally-acquired HSV meningoencephalitis, which is usually caused by primary infection with HSV-2; and HSV in immunocompromised children.

### Herpes Simplex Virus Encephalitis

**Pathophysiology of HSV encephalitis**

At least 90% of HSV encephalitis cases are caused by HSV-1. Following primary infection of the orofacial skin and mucosa, latent infection persists in the trigeminal ganglion and olfactory bulb in a proportion of children. Some encephalitis cases (especially in infants and the immunocompromised) occur as part of the primary infection, but in around 70% of cases anti-HSV IgG is detectable at presentation (Whitley 2002), suggesting reactivation of previously encountered infection. Entry to the CNS is via retrograde neuronal transport along the olfactory nerve or meningeal branches of the trigeminal nerve. The finding of dormant HSV in the brain at one-third
of autopsies following road traffic accidents suggests reactivation of virus already established in the CNS in a significant proportion of encephalitis cases. Regardless of the latent site, the cause or trigger of HSV reactivation is not known (Thompson et al. 2012). Recent research suggests susceptibility to HSV encephalitis may be inherited as an autosomal recessive defect in the TLR3-interferon innate immune response, which confers CNS protection against primary HSV-1 infection in healthy children (Rozenberg 2013; Zhang et al. 2013).

Neurotropism in HSV encephalitis for the basal frontal, mesial temporal, cingulate and insular cortex may be explained by proximity of these cortical areas to the termination of the olfactory fibres. HSV encephalitis is highly cytopathic, pathologically characterised by necrotic lesions, which are often haemorrhagic with gross softening, and in severe cases, loss of all neural and glial elements (Barnes and Whitley 1986). Intranuclear eosinophilic inclusions (Cowdry type A bodies) are recognised in neurons and glia.

**Clinical features of HSV encephalitis**

HSV encephalitis classically presents as an acute illness characterised by fever and encephalopathy together with behavioural disturbances and/or motor deficits and/or convulsions (Ward et al. 2012). However, in many cases the clinical features of HSV encephalitis are not characteristic; the disease cannot be reliably distinguished, on clinical presentation alone, from other less severe infections. The full clinical picture is preceded in 60% of cases by prodromal symptoms that may be purely systemic, such as fever and malaise, or may be more characteristic of encephalitis, with disturbances of behaviour. Subtle changes in speech, memory or sensation may precede the more severe neurological signs by several days. Labial herpetic lesions (cold sores) are observed in 7–25% of children (Elbers et al. 2007).

The end of the prodromal phase is marked by worsening symptoms of reduced consciousness, abnormal behaviour and high fever. The full-blown picture includes symptoms common to many encephalitides, that is, lethargy, obtundation or coma and convulsive seizures. Seizures are particularly frequent and often recurrent in HSV, and they are almost always focal, manifesting especially in the face and upper limbs. Unilateral status epilepticus may also occur. In infants and young children febrile seizures are often the dominant symptom; children below the age of 3 years had convulsive seizures in every case of HSV encephalitis in one series, while older children demonstrated a broader range of presentations (Ward et al. 2012). In some younger children, febrile seizures may be the only symptom for several days. Such cases pose a significant diagnostic challenge.

Other neurological manifestations include hemiplegia and aphasia, which can be a prominent and early finding in older children and adolescents. An acute opercular syndrome has been described, in which bilateral disturbance of facio-linguo-glossopharyngeal control leads to orofacial palsy, dysarthria and dysphagia (Garcia-Ribes et al. 2007). Changes pointing to focal necrosis of the temporobasal structures such as anosmia, olfactory hallucinations and disordered behaviour may be prominent (Whitley et al. 1981). Raised intracranial pressure is a common complication of HSV encephalitis and papilloedema is present in approximately 15% of cases. Atypical presentations of HSV include a brainstem encephalitis variant with cranial nerve involvement (Duarte et al. 1994) and acute myelitis (Wiley et al. 1987). The latter is seen mainly with HSV-2. Cases of severe temporal lobe epilepsy have also been attributed to smouldering HSV-2 infection (Cornford and McCormick 1997).

Mild HSV encephalitis has been reported in a few children who presented with fever and seizures or other neurological symptoms in the absence of encephalopathy, and enjoyed a favourable outcome (Elbers et al. 2007). However, such cases are rare.

**Diagnosis of HSV encephalitis**

The detection of herpes simplex virus DNA in the CSF by PCR is the mainstay of HSV encephalitis diagnosis. One series of biopsy-proven cases found PCR diagnosed HSV encephalitis with 96% specificity and 99% sensitivity (Lakeman and Whitley 1995). The initial approach to diagnosis in suspected viral encephalitis, including considerations regarding timing of lumbar puncture and early neuroimaging, and guidance regarding interpretation of a negative PCR result, is covered in Diagnosis in the Viral Encephalitis section.

Other investigations may support the clinical diagnosis of HSV encephalitis before the PCR result is available. CSF pleocytosis is usually observed, but the CSF is normal in 20–25% of patients, particularly in samples taken in the first few days of illness. In most cases, CSF is under moderately increased pressure and contains an excess number of cells, usually lymphocytes, from tens to hundreds per mm³. The CSF is frequently haemorrhagic or xanthochromic, with an elevation of red cells in 50% of cases (Novak 1984), usually in younger children (Ward et al. 2012). CSF protein is typically mildly elevated with normal glucose (Kennedy 2004).

EEG is abnormal in 86% of children with HSV encephalitis (Lahat et al. 1999). EEG commonly demonstrates periodic lateralised epileptiform discharges between the second and fifteenth day of disease (Schauseil-Zipf et al. 1982) (Fig. 11.14). These were once thought diagnostic of HSV encephalitis but are now known to occur in other encephalitides also (Hulihan et al. 1992, Garcia-Morales et al. 2002). Other nonspecific EEG abnormalities in HSV encephalitis include generalised and focal high amplitude slow waves and temporal spike-and-wave activity. Low amplitude may be observed in one or more regions. Tracings are usually very asymmetrical.

Neuroimaging may appear normal in the first 24–48 hours after disease onset. Early CT is abnormal in 25–80% of patients (Raschilas et al. 2002), showing reduced attenuation in one or both frontal or temporal lobes, and sensitivity is increased with use of intravenous contrast; however, CT alone is inadequate for diagnostic imaging in HSV encephalitis. Diffusion-weighted MRI is the most sensitive modality for early
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detection of HSV encephalitis (McCabe et al. 2003, Sawlani 2009). The main pattern is of bilateral, asymmetrical changes (gyral oedema on T1-weighted imaging and hyperintensity on T2-weighted imaging) in the medial temporal lobe and other limbic structures, the inferior frontal lobes, insula and cingulate gyrus (Fig. 11.17). The parietal lobes and other extra-temporal regions may be involved in up to 59% of cases (To et al. 2014), particularly in younger children (Ward et al. 2012). The lentiform nucleus, and basal ganglia more generally, are characteristically spared. The differential diagnosis of bilateral temporal lobe hyperintensity includes neurosyphilis, mesial temporal sclerosis, and mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (Sureka and Jakkani 2012). Involvement of the cingulate gyrus and contralateral temporal lobe is highly suggestive of HSV encephalitis (Steiner et al. 2005). Diffusion-weighted MRI may demonstrate restricted diffusion in areas appearing normal on conventional MRI (Kuker et al. 2004). Early findings of focal gyral oedema on T1-weighted imaging progress to extensive cortical necrosis, with or without haemorrhagic changes, and later atrophy of affected areas. Focal HSV encephalitis with pseudotumoural features has been reported (Counsell et al. 1994). Additional MRI sequences may be useful in some cases, including susceptibility-weighted imaging for early haemorrhagic foci, post-gadolinium imaging for gyriform enhancement, and magnetic resonance spectroscopy for metabolic changes of neuronal death (Sureka and Jakkani 2012). Resolution of the latter with time has been proposed as a marker of treatment efficacy (Steiner et al. 2005).

In patients without a PCR sample taken in the first 10–12 days of illness, demonstration of a four-fold rise of antibody titre against HSV-1 in the CSF may be considered supportive of the diagnosis of HSV encephalitis in the correct clinical context. However, the change in antibody titre takes at least 10–14 days to appear (Koskineniemi et al. 1984). The antibodies initially belong to the IgM class and later switch to IgG type. They are associated with the presence of an oligoclonal protein pattern in the CSF (Mathiesen et al. 1988). The antibodies and oligoclonal pattern may persist for years following the acute infection (Tardieu and Lapresle 1980).

Management of HSV encephalitis
The initial and supportive management, including commencement of aciclovir and dosing, is covered in Management in the Viral Encephalitis section. This section concerns management of PCR-confirmed HSV encephalitis. Aciclovir remains the treatment of choice for HSV encephalitis, with significant benefits in reducing both mortality and morbidity (James et al. 2009). Its mechanism of action, requiring phosphorylation to the active form by viral thymidine kinase before competitive inhibition of viral DNA polymerase can occur, means that it works most efficiently during early viral replication (Crawford 2010). It is therefore important to start treatment promptly when HSV encephalitis is suspected.

Aciclovir-resistant strains of HSV are rarely encountered in children, except in those with multiple previous exposures to the drug. In general, children tolerate aciclovir very well, although at high doses aciclovir may cause renal toxicity if the patient is not well hydrated. A course of at least 14–21 days intravenous aciclovir is required in proven HSV encephalitis (Kneen et al. 2012). Shorter courses are associated with up to 26–29% relapse rate: younger children and infants appear to be at greatest risk (Ito et al. 2000; Love et al. 2004; Valencia et al. 2004). Some advocate a 21-day course for children younger than 12 years (Thompson et al. 2012). Switching to

Figure 11.17  (a) MRI coronal fluid attenuated inversion recovery and (b) T2-weighted axial images showing hyperintensity in the right insular cortex and frontal operculum secondary to herpes encephalitis. (Courtesy of Dr K Mankad, Great Ormond Street Hospital, London, UK.)
oral valaciclovir, a prodrug with superior bioavailability compared to oral aciclovir, may be considered after at least 10–14 days of intravenous treatment (Chan et al. 2000). Repeat lumbar puncture at end of treatment is recommended to demonstrate treatment efficacy with a negative PCR result; if the CSF remains HSV positive, aciclovir should be continued with weekly CSF PCR until the result is negative (Cinque et al. 1996; Tunkel et al. 2008; Kneen et al. 2012). Discussion with a specialist in virology or infectious diseases is also suggested in such cases to consider revised antiviral therapy (Tyler 2004).

Experimental and clinical observations suggest a benefit from adjunctive corticosteroid therapy in HSV encephalitis but evidence is not yet sufficient to recommend this as standard practice (Ramos-Estebanez et al. 2014). Corticosteroids may be used by specialists for specific circumstances including marked cerebral oedema, brain shift or raised intracranial pressure (Kneen et al. 2012). The Corticosteroids in HSV Encephalitis (COHESIVE) randomised controlled trial started recruiting British adults in 2014 and the outcome of the European GACHE trial is also awaited (Martinez-Torres et al. 2008).

Relapse of HSV encephalitis
Clinical relapse may occur in up to a quarter of HSV encephalitis cases (De Tiege et al. 2003) and has been described up to 8.5 years after the initial episode (Spiegel et al. 2008). In some cases relapse is due to continuing viral replication in the CNS, for example associated with absence of HSV antibody production in the CSF (De Tiege et al. 2006) However, in most cases there is no molecular evidence of viral reactivation (Hacohen et al. 2014), suggesting an immune-mediated mechanism may be responsible (De Tiege et al. 2003; Skoldenberg et al. 2006). A characteristic clinical picture of encephalopathic relapse with prominent choreoathetoid movement disorder and seizures, associated with white matter changes on MRI and poor prognosis, is well recognised following HSV encephalitis (Barthez et al. 1987; Shanks et al. 1991; Wang et al. 1994; De Tiege et al. 2003; Valencia et al. 2004; Kullnat and Morse 2008); more recently, anti-NMDA receptor antibodies have been detected in some cases (Leypoldt et al. 2013, Pruss 2013, Hacohen et al. 2014). Immunomodulation plus empirical antiviral therapy may maximise neurorehabilitation potential in such patients. An approach to management has been proposed in which cases negative for ongoing HSV replication (as determined by CSF with or without blood PCR) are treated with IVIg or plasmapheresis. Steroids and other immunosuppressive drugs may be used as second-line therapy, with careful surveillance for virological reactivation (Bamford et al. 2014).

Outcome of HSV encephalitis
In the pre-aciclovir era, mortality from HSV encephalitis was greater than 70%, and less than 3% survived without severe sequelae. In the aciclovir era, mortality in children is 6–8% (Whitley et al. 1986; Ito et al. 1998; Lahat et al. 1999) but morbidity remains high, with 36–79% of survivors suffering long-term sequelae (Ito et al. 1998; Lahat et al. 1999; Elbers et al. 2007; Ward et al. 2012). Common sequelae include developmental delay and cognitive impairment (15–58%), seizures (15–44%), motor deficits (19–37%), visual loss (21%), personality change and behavioural problems (5–15%) and speech difficulties (5–7%) (Lahat et al. 1999; Elbers et al. 2007; Ward et al. 2012). Severe epilepsy in infants may manifest as infantile spasms.

Outcome is difficult to predict during the acute illness. Table 11.12 summarises some of the reported prognostic factors. Sequelae are more common in younger children (Ito et al. 1998; Lahat et al. 1999; Whitley and Kimberlin 2005; Ward et al. 2012) and in those with greater impairment of consciousness at presentation (Whitley et al. 1986; Lahat et al. 1999). One study found mean GCS at presentation in patients later suffering neurological sequelae was 7.7, compared to 11 in those without sequelae (Lahat et al. 1999). Late administration of aciclovir (McGrath et al. 1997; Raschilas et al. 2002) and status epilepticus during the acute illness (Herrmann et al. 2006) are also associated with poorer outcome. High viral load in the CSF has also been proposed as a negative prognostic feature (Domingues et al. 1998), but a direct relationship between HSV DNA copies per millilitre of CSF and CNS damage has not so far been established (Tyler 2004).

Herpes simplex virus meningitis
Aseptic meningitis without encephalitis is more commonly caused by HSV-2 than HSV-1. It is rare in children. HSV-2 meningitis may be a manifestation of primary infection in the sexually active adolescent; in younger children the possibility of sexual abuse should be considered. Rarely, mild cases of HSV-1 infection can manifest only with meningeal irritation (Whitley et al. 1982), with recovery in 7–14 days. Around 20% of HSV-2 meningitis patients develop recurrent episodes termed Mollaret meningitis. This rare, benign meningitis is characterised by multiple episodes of aseptic, lymphocytic meningitis separated by symptom free periods. Transient neurological symptoms are described but no permanent neurological sequelae. Treatment of Mollaret meningitis is with intravenous aciclovir followed by oral valaciclovir prophylaxis. Indomethacin has also been tried to speed recovery.

Perinataly-acquired herpes simplex virus
Neonates with HSV infection usually acquire it by vertical transmission during birth; hence, HSV-2 (which causes genital herpes) has been the predominant cause of disseminated HSV infection and meningoencephalitis in this age group (Kennedy and Chaudhuri 2002), although HSV-1 is becoming more important in some developed settings (Jones et al. 2014). The disease is devastating in the neonatal period. In 70% of cases infection is acquired from an asymptomatic mother, and occasionally from other caregivers in close contact with the child during the neonatal period (Brown 2004). Risk factors for vertical transmission include maternal primary infection during the third trimester, invasive monitoring.
during labour, vaginal delivery, gestation less than 38 weeks, and maternal age less than 21 years (Whitley 2004). Maternal seropositivity to HSV-1 or HSV-2 is protective. Vertical transmission may be decreased by prophylactic antiviral treatment (Berardi et al. 2011).

Presentation may be delayed until 2–4 weeks after birth. CNS involvement occurs in 30% of all infected neonates, rising to 70% in those with disseminated infection (Berger and Houff 2008). Presentation is typically with seizures (focal or generalised), irritability, lethargy and/or fever (Baskin and Hedlund 2007). Skin lesions are observed in two-thirds of infants.

**Diagnosis of perinatally-acquired HSV infection**

Basic principles of initial investigation and management are as outlined in Management in the Viral Encephalitis section. Laboratory results in disseminated disease often show abnormal liver function and disseminated intravascular coagulation. CSF typically shows a lymphocytic pleocytosis, increased protein levels, and PCR positivity for HSV-2 (Berger and Houff 2008). The presence of a multifocal periodic pattern on the EEG, together with an inflammatory CSF, is highly suggestive of herpetic encephalitis and may occur before any abnormality is visible on CT or MRI. Neuroimaging changes in perinatally-acquired HSV are more diffuse and widespread than in older children (Steiner et al. 2005), presumably due to haematogenous rather than neuronal mechanism of CNS penetration. The temporal and frontal lobes may be spared with lesions seen instead in the deep grey and periventricular white matter. Lesions show nonspecific diffuse hypointensity on T1-weighted imaging and hyperintensity on T2, and are rarely haemorrhagic (Schneider 2011). Restricted diffusion in the periventricular area is a sensitive marker of early disease (Dhawan et al. 2006).

**Management of perinatally-acquired HSV infection**

Randomised controlled trial evidence in neonatal HSV encephalitis shows high-dose intravenous aciclovir (20mg/kg 8 hourly) for 21 days decreases mortality and morbidity (Kimberlin et al. 2001) and is the recommended treatment regimen (Thompson et al. 2012). This high dose of aciclovir is associated with a mild degree of neutropenia in most patients, which if more severe could be supported by granulocyte colony stimulating factor. In view of the more extensive and diffuse CNS infection and less mature immune response in neonates, repeat CSF PCR at the end of intravenous treatment is strongly advised to confirm viral clearance (Kimberlin 2004). Quantitative PCR (see Box 11.1) can be used as a guide to treatment efficacy (Thompson et al. 2012). Prolonged oral suppression therapy may have a role in reducing the incidence of recurrent disease (Tiffany et al. 2005). However, aciclovir resistance has been reported in some cases of prolonged therapy (Thompson et al. 2012).

**Outcome of perinatally-acquired HSV infection**

Mortality in neonatal HSV encephalitis has reduced from 50% in the pre-aciclovir era to 4% with high-dose aciclovir (James et al. 2009). Unfortunately neurodevelopmental outcomes remain devastating with two-thirds suffering sequelae including diffuse cystic encephalomalacia, microcephaly, seizures, cerebral palsy and cognitive impairment (Schneider 2011). Prognosis is better in HSV-1 than HSV-2.

**Herpes simplex virus in immunocompromised children**

Primary HSV infection in the immunocompromised may be life threatening. The mouth, skin, lungs and gut are most often affected; the CNS is rarely specifically involved. However, a high index of suspicion is required; an atypical subacute presentation is described in immunocompromised children (Kleinschmidt-DeMasters and Gilden 2001) and CSF pleocytosis may be absent. CSF PCR is therefore crucial in diagnosis and monitoring of treatment (Cinque et al. 1998). High-dose intravenous aciclovir should be effective, although resistance may be problematic for immunocompromised patients (Wilson et al. 2009), especially those with repeated exposure to oral treatment. Such cases may require treatment with other antivirals such as foscarnet or cidofovir (Whitley 2002).

**Varicella Zoster Virus**

VZV infection is transmitted by droplets entering the body via the respiratory tract or conjunctiva. Primary infection is associated with a range of CNS complications occurring in around one to two per 10,000 childhood cases (Stahl et al. 2011), with a particular tendency to cause large and small vessel vasculopathy. Quantification of VZV DNA in the CSF has demonstrated higher levels in those with more severe disease (Aberle et al. 2005). As with other alphaherpesviruses, latent infection is established in the sensory ganglia; however, CNS manifestations of reactivated VZV are rare in children, with the exception of the immunocompromised (Koskineni et al. 2002).

Neurological manifestations may occur simultaneously with chickenpox or many months later; in some cases they may precede vesicular eruption, or even occur in patients with no rash (Gnann 2002). Four distinct CNS presentations are recognised: acute aseptic meningitis, acute encephalitis, post-infective cerebellitis, and post-infective focal arteritis manifesting as stroke. It has been argued that all CNS presentations of VZV are best thought of as variable manifestations of a common pathogenic mechanism of vasculopathy (Baskin and Hedlund 2007). VZV may also cause ventriculitis, benign idiopathic intracranial hypertension (Ravid et al. 2012) and Reye syndrome (see Reye Syndrome section) (Hurvitz et al. 1982). Superadded bacterial infection should be considered in the differential diagnosis of VZV-associated CNS disease, as the virus is known to cause transient immunosuppression.

**Aseptic meningitis**

VZV not uncommonly causes symptoms evocative of meningitis (photophobia, headache) without any evidence of CNS involvement (Stahl et al. 2011). Lumbar puncture may
reveal the presence of VZV by PCR, with or without pleocytosis and/or elevated protein. Acellular CSF occurs more commonly in patients with immunocompromise (Studahl et al. 2000). In immunocompetent children VZV meningitis is largely self-limiting. Aciclovir may be considered in PCR-positive cases with ongoing symptoms.

**VZV-associated acute encephalitis**

Although commonly referred to as an encephalitis, the acute encephalopathy occurring in association with VZV infection may be more properly described as a multifocal vasculopathy or leukoencephalopathy (Gilden 2002; Baskin and Hedlund 2007). The clinical features are those of a nonspecific viral encephalitis, ranging in severity from mild confusion and headache to seizures, reduced consciousness and focal neurological deficits (Baskin and Hedlund 2007). Onset may be acute or subacute (Kneen et al. 2012). Onset prior to eruption of vesicles has also been described (Maguire and Meissner 1985; Wagner et al. 1998). The immunocompromised are particularly susceptible (Koskineni et al. 2002), and it may occur as part of a VZV reactivation with cranial dermatome involvement (shingles) and/or disseminated infection. Stroke and myelitis may complicate the picture further.

MRI demonstrates diffuse, multifocal cortical and subcortical hypointensity on T1-weighted imaging with high signal on T2 (Baskin and Hedlund 2007). In immunocompromised children the distribution may be more clearly arterial. MRA should be performed to look for evidence of vasculitis (Nagel et al. 2008). CSF should be sent for PCR; CSF IgG detection can be useful in cases where PCR result is negative or not available.

VZV encephalitis should be treated with intravenous aciclovir at a dose of 500mg/m² (ages 3 months to 12 years) or 10–15mg/kg (age >12 years) three times daily for up to 14 days (Kneen et al. 2012). Adjunctive corticosteroids may be given (Solomon et al. 2007).

**VZV-associated post-infective cerebellitis**

VZV-associated cerebellitis is usually mild, presenting as acute ataxia in a younger child with a history of recent chickenpox infection. Although described as post-infective, ataxia may in fact occur prior to eruption of chickenpox vesicles (Dangond et al. 1993). Most cases show full recovery within a few weeks and no specific treatment is required (Kneen et al. 2012). Hydrocephalus may occur secondary to cerebellar swelling in severe cases (Shkalim et al. 2009). Where neuroimaging is performed this should include MRA for vasculopathy.

**VZV-associated post-infective vasculopathy**

There is a four-fold increased risk of arterial ischaemic stroke in the 0–6 months after chickenpox (Thomas et al. 2014). VZV is thought to account for up to one-third of all arterial ischaemic stroke in children (Kneen et al. 2012). Children are usually immunocompetent and previously well (Baskin and Hedlund 2007). Median interval between chickenpox and stroke is 4 months. Infarction typically occurs in the middle cerebral artery territory secondary to abnormalities in the M1 segment of that vessel (Miravet et al. 2007). There is probably more than one mechanism for these post-infectious events, and inflammatory changes in arterial tissue as well as increased secretion of procoagulants such as anticardiolipin may be important in some cases (Kurugol et al. 2000, 2001). In addition, the host immune response to VZV includes antibodies that may cross-react with and inactivate the important host anticoagulant factor protein S. This may lead to a hypercoagulable state with development of purpura fulminans as well as post-VZV ischaemic stroke (Josephson et al. 2001; Thomson et al. 2010). Haemorrhagic infarcts are also reported (Gilden et al. 2009).

Presentation is usually with acute onset of hemiparesis, chorea or facial weakness (Kneen et al. 2012). MRI with angiogram is usually diagnostic of a focal or multifocal arteriopathy with irregularity, segmental narrowing, beading, or stenosis of the anterior and middle cerebral arteries and their branches. Isolated basal ganglia ischaemia is also described and may be unilateral or bilateral (Baskin and Hedlund 2007) (Fig. 11.18). Extensive investigation for causes of arterial ischaemic stroke should be carried out as detailed in Chapter 15; treatable risk factors may co-exist with VZV arteriopathy in some patients (Miravet et al. 2007). Workup should also include lumbar puncture; detection of anti-VZV IgG in the CSF (positive in 93% of cases) is more sensitive than VZV PCR, which is only positive in 30%. CSF pleocytosis is usually absent. Intrathecal synthesis of IgG can be confirmed by reduced serum/CSF ratio (Nagel et al. 2008). One-quarter of patients suffer recurrence which is usually associated with progressive arteriopathy (Miravet et al. 2007).

**Epstein–Barr Virus**

Infection with Epstein–Barr virus (EBV) occurs mainly via the oropharyngeal route. Most children are infected asymptotically in early life; those infected later may present symptomatically with infectious mononucleosis. Various neurological complications of infection with this B-cell lymphotropic herpesvirus are reported and may be less rare than previously thought, occurring in up to 5% of infectious mononucleosis cases in teenagers and young adults (Junker 2005). CNS manifestations range from aseptic meningitis and cranial neuropathies to fulminant encephalitis which can mimic HSV encephalitis (Whitley et al. 1989). EBV encephalitis in the immunocompetent occurs mainly as an immune-mediated complication of primary infection (Stahl et al. 2011). The virus may be implicated in up to 10% of all acute encephalitides in children, and co-infection with other agents (particularly *Mycoplasma pneumoniae*) is common (Weinberg et al. 2005; Doja et al. 2006). Neurological presentations also occur in the context of reactivated infection, with serious long-term complications including hippocampal atrophy and sclerosis (Hausler et al. 2002).
EBV ACUTE ENCEPHALITIS
EBV encephalitis in the immunocompetent is most common in teenagers, with a median age of 13 years. Only 5–18% of patients have a clear preceding history of infectious mononucleosis but nonspecific prodromal symptoms of fever and headache are common (Doja et al. 2006). Neurological illness classically presents 1–3 weeks after the prodromal illness (Schnell et al. 1966; Greco et al. 2014) although some patients go on to develop symptoms of infectious mononucleosis following initial presentation with isolated neurological symptoms (Booss and Esiri 2003). Encephalopathy may be profound. Around half of children suffer seizures; presentation may be with acute status epilepticus (Connelly and DeWitt 1994). Nonconvulsive status epilepticus is also reported (Greco et al. 2014). Other neurological features include focal motor deficits and hallucinations. Transverse myelitis and optic neuritis may be associated in some cases (Doja et al. 2006). Cerebellar involvement is common and may rarely result in obstructive hydrocephalus. Brainstem involvement is rarely observed (Baskin and Hedlund 2007) and can present with signs and symptoms mimicking a tumour (Angelini et al. 2000).

Diagnosis of EBV encephalitis
CSF pleocytosis is usually observed with variable patterns of neutrophil and lymphocyte predominance (Bathoorn et al. 2011). EBV DNA is detectable by PCR in around half of cases. Acute and convalescent serology may be helpful in PCR-negative cases; detection of anti-EBV IgM or rising IgG is more sensitive and specific than heterophile antibodies. EEG may show generalised or focal slowing, epileptiform discharges and focal intermittent rhythmic delta activity (Doja et al. 2006). Neuroradiological findings are observed in up to 80% of cases (Doja et al. 2006). The characteristic pattern is of increased T2-weighted signal in the bilateral thalami and basal ganglia. Multifocal lesions may also be seen in the cerebral cortex, brainstem and cerebellum. Diffusion is not restricted. Magnetic resonance spectroscopy may be helpful especially in cases with basal ganglia involvement (Baskin and Hedlund 2007). White matter involvement with demyelination is a feature in some cases (Doja et al. 2006).

MANAGEMENT AND OUTCOME OF EBV ENCEPHALITIS
Management of EBV encephalitis remains largely supportive. Antiviral therapy with aciclovir or ganciclovir has been tried, as these agents show activity against the virus in vitro (Doja et al. 2006), but there is little clinical evidence to support this (Baskin and Hedlund 2007). Corticosteroids have been used in ADEM-like presentations and fulminant infectious mononucleosis (Andersson and Ernberg 1988). EBV encephalitis may be fatal, particularly in those with status epilepticus, but the majority of patients make a full recovery (Doja et al. 2006). Thalamic and limbic involvement is associated with poorer outcome (Abul-Kasim et al. 2009). Convalescence may be prolonged (weeks to months) and fatigue is a common persisting symptom. Other sequelae include behavioural change and focal motor deficits (Domachowske et al. 1996).

OTHER CENTRAL NERVOUS SYSTEM PRESENTATIONS OF EBV INFECTION
EBV may cause aseptic meningitis with or without cranial nerve involvement (Hausler et al. 2002), affecting primarily the VIIth nerve (Bell’s palsy) but also the optic and hypoglossal nerves. EBV-associated optic neuritis may be unilateral or bilateral; it is usually retrobulbar, but may also involve the chiasm (Beiran et al. 2000; Baskin and Hedlund 2007). The ‘Alice in Wonderland’ syndrome (Todd 1955) of perceptual distortions regarding the size, shape and colour of objects...
(visual metamorphosia) is described in association with EBV infection (Lahat et al. 1990; Cinbis and Aysun 1992; Hauser et al. 2002). Acute onset of parkinsonism with subsequent full recovery is also described (Hsieh et al. 2002). EBV is suspected to play a key role in the pathogenesis of multiple sclerosis (Ascherio and Munger 2007), with the small proportion of the population not exposed to EBV strongly protected against multiple sclerosis, and those suffering infectious mononucleosis at greater than two-fold increased risk (Thacker et al. 2006).

**Epstein–Barr virus in immunocompromised children**

Viral reactivation is the likely aetiology when EBV CNS disease occurs in the immunocompromised. CSF is more likely to be acellular (Studahl et al. 2000). Very high levels of EBV DNA may be detected in the CSF in immunocompromised patients with CNS lymphoma (Weinberg et al. 2002). EBV-driven lymphoma is particularly associated with advanced HIV disease and may present as isolated CNS involvement or multisystem disease (Nadal et al. 1994). More effective treatments for EBV-driven lymphoma in HIV, including antiretroviral therapy, chemotherapy and immune modulators such as rituximab are now available.

EBV infection may be responsible for a severe and often fatal illness in certain families in which host susceptibility to EBV is transmitted as an X-linked character. This disease is known as the X-linked lymphoproliferative (XLP) syndrome (Grierson and Purtilo 1987) and variably features fatal infectious mononucleosis, malignant lymphoma, acquired hypo- or agammaglobulinaemia, and virus-associated haemophagocytic syndrome (Tiab et al. 2000; Gilmour and Gaspar 2003). The gene defective in XLP has been identified and designated **SH2D1A**. It encodes an adaptor protein SAP [signalling lymphocytic activation molecule-associated (SLAM-associated) protein] and measurement of this protein can be used to diagnose the condition (Gilmour et al. 2000). XLP is associated with a high morbidity, and overall outcome is poor. At present, allogeneic stem cell transplantation is the only curative treatment (Lankester et al. 2005).

A similar syndrome of mono- or poly-clonal lymphocyte proliferation driven by EBV, known as post-transplant lymphoproliferative disease (PTLD), may occur in immuno-suppressed patients, especially in transplant recipients (Randhawa et al. 1992). Post-transplant lymphoproliferative disease may present with multi-organ involvement, infrequently including the CNS. Brain involvement in transplant recipients with post-transplant lymphoproliferative disease carries a poor prognosis; however, isolated CNS involvement has a better prognosis than CNS plus extracranial involvement (Buell et al. 2005). It has been demonstrated, in a study of paediatric liver transplant patients, that monitoring of EBV viral load with early intervention can reduce the incidence of post-transplant lymphoproliferative disease (Lee et al. 2005). Combination treatment with antiviral therapy and the anti-B-cell monoclonal antibody rituximab has some efficacy (Nozzoli et al. 2006) and immunosuppression is reduced where possible.

**Cytomegalovirus**

Cytomegalovirus (CMV) is a major cause of congenital CNS infection, as described in Chapter 1. Postnatally acquired CMV is highly prevalent with 50–80% of the population seropositive in adulthood (Stahl et al. 2011). Primary infection is usually asymptomatic although an infectious mononucleosis-type illness may occur. The most important postnatally acquired CNS manifestation is encephalitis, which occurs almost exclusively in the immunocompromised (Arribas et al. 1996), in the context of systemic CMV reactivation. There is usually a high viral load in the blood, and end organ disease may occur in the brain, retina, lungs, bone marrow, liver and gut. Encephalitis may be generalised, with fever, headache and altered consciousness, or focal, with ventriculo-encephalitis, cerebral mass lesions and cranial neuropathies, especially in patients with HIV (Baskin and Hedlund 2007). CSF may be neutrophilic with low glucose, or acellular (Studahl et al. 2000); diagnosis relies on detection of cytomegalovirus DNA in the CSF by PCR. Neuroimaging may show cortical and subcortical areas of T2 hypointensity in the frontal and parietal lobes (Baskin and Hedlund 2007). Subependymal gadolinium enhancement is sometimes observed (Crawford 2010).

Other CNS manifestations of CMV in the immunocompromised host include cranial nerve palsies, transverse myelitis, radiculitis and retinitis. CMV retinitis is well recognised in advanced HIV infection; where this occurs in infants in contrast to adults or older children, the macula rather than the peripheral retina is first affected, causing immediate risk to central vision (Wren et al. 2004). CMV disease in the CNS, including retinitis, may become acutely symptomatic in patients with HIV once they start antiretroviral therapy as a manifestation of immune reconstitution inflammatory syndrome (IRIS). IRIS is more common in patients who start treatment with advanced disease and very low CD4 counts, and it requires careful management with treatment of the CMV, HIV and immune modulation to reduce symptoms (Griffiths 2004). There is also increasing interest in the role of CMV in neuro-oncogenesis following detection of the virus in a high proportion of glioblastomas (Baryawno et al. 2011) and medulloblastomas (Miller 2009; Lucas et al. 2011), with possible implications for pathogenesis and treatment (Soderberg-Naucler and Johnsen 2015).

Treatment of CNS cytomegalovirus with gancyclovir, foscarnet or cidofovir may be effective (Avila-Aguero et al. 2003); however, these are toxic agents and require close monitoring. Ganciclovir is the first-line compound used, followed by foscarnet and cidofovir; longer-term oral maintenance suppressive therapy can be considered with oral valganciclovir (Kimberlin 2002; Griffiths 2004). Success of therapy is monitored by end organ response as well as blood viraemia level. Prognosis is guarded without improved immune function.
Rare cases of meningoencephalitis in immunocompetent children are usually self-limiting.

**Human Herpes Viruses 6 and 7**

The overwhelming majority of children around the world become infected with human herpes viruses 6 (HHV-6) and 7 (HHV-7) in the first two years of life (Caserta et al. 2001). Viral entry and shedding is via the salivary glands and latency is established in the salivary glands, T lymphocytes and brain. Primary infection is asymptomatic in many children (Stahl et al. 2011). HHV-6 comprises two closely related species, HHV-6A and HHV-6B; the latter is well known as the cause of exanthem subitum (roseola infantum), and is also a major cause of febrile convulsions in children under two years of age. A small proportion of children infected with HHV-6 develop meningoencephalitis as an acute or (rarely) post-infective complication of primary infection. The natural history of primary infection with HHV-7 is less well understood, but may also be associated with exanthem subitum and CNS involvement (Ward 2005).

**HHV-6 Meningoencephalitis**

HHV-6 is implicated as a cause of viral encephalitis (Yao et al. 2009). Disease can be severe with ataxia and prolonged convulsions (Manninen et al. 2007). Diagnosis is challenging because HHV-6 is able to integrate into chromosomes in a significant proportion of the population, leading to chronic presence of high levels of viral DNA in CSF and other body fluids (Kneen et al. 2012), which may need to be excluded in suspected cases of HHV-6 meningoencephalitis. Quantitative PCR in blood and CSF can help distinguish acute infection from chromosomal integration (Ward et al. 2007). HHV-6 antibody reactivity in the CSF and peripheral seroconversion also support acute over latent infection. Neuroimaging may be normal or demonstrate abnormalities in the frontal lobes, medial temporal lobes, hippocampi and limbic system. Changes include oedema and increased T2 signal on MRI, usually without restricted diffusion (Baskin and Hedlund 2007). Treatment with ganciclovir or foscarnet may be effective for confirmed cases (Solomon et al. 2007; Tunkel et al. 2008). Sequelae include persistent volume loss in the medial temporal lobes. HHV-6 has been frequently associated with parainfectious encephalopathy syndromes including acute necrotising encephalopathy (see section Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses); changes affecting the basal ganglia, striatum, thalami and brainstem have been described (Baskin and Hedlund 2007).

Febrile convulsions occur in up to 36% of primary HHV-6 infection in younger children (Hall et al. 1994). A UK prospective study of children under 3 years of age presenting with febrile convulsions found 17% had primary infection with either HHV-6 or HHV-7 (Ward et al. 2005). HHV-6B is particularly associated with febrile convulsions and in some cases is isolated from the CSF (Theodore et al. 2008). HHV-6B is also implicated in mesial temporal lobe epilepsy; one series of children undergoing surgical resection for mesial temporal lobe epilepsy found evidence of active HHV-6B replication in almost half the samples (Fortheringham et al. 2007).

**Human herpes viruses 6 and 7 in immunocompromised children**

HHV-6 reactivation occurs commonly in the immunocompromised, including nearly 50% of bone marrow recipients and 20–30% of solid organ transplant recipients. Complications appearing 2–3 weeks following the procedure may include fever, rash, pneumonia, bone marrow suppression, graft rejection (Yoshikawa 2003) and, rarely, encephalitis. Symptoms of the latter include altered consciousness, seizures and headache. Prompt treatment with ganciclovir or foscarnet reduces mortality (Singh and Paterson 2000). HHV-6 is the major cause of post-transplant acute limbic encephalitis (PALE) (Seeley et al. 2007). Development of limbic encephalitis is associated with high viral load post-transplant (Ogata et al. 2006). HHV-7 viraemia after stem cell transplant has also been associated with encephalitis (Chan et al. 2004).

**Enteroviruses**

Enteroviruses are small, single-stranded RNA viruses in the *Picornavirus* family. Most enterovirus infections are asymptomatic but they also cause a range of common and mostly benign illnesses in children worldwide. Neurological involvement occurs in a small proportion of cases, ranging from self-limiting aseptic meningitis to poliomyelitis and brainstem encephalitis with significant morbidity and mortality.

A revised taxonomy of enteroviruses based on genomic analysis names 12 species (enteroviruses A to J and rhinoviruses A to C) within the genus. However, the 90 plus serotypes identified to date (Abzug 2014) are usually organised for clinical purposes into the traditional groupings of coxsackie viruses (A and B), echoviruses, polioviruses and the numbered enteroviruses. The spectrum of tropism for each enterovirus is considerable and many can cause neurological disease (Rhoades et al. 2011).

Transmission of enteroviruses is usually via the faecal–oral route although respiratory transmission also occurs. Neonates can acquire infection perinatally via the ascending or transplacental routes, during delivery, and possibly postpartum from breast milk (Tebrugge and Curtis 2009). Enteroviruses can survive on household surfaces at room temperature for several days. After replication in the gastrointestinal or respiratory lymphatic tissue during an incubation period lasting 3–10 days, the virus may cause one or more periods of viraemia, leading to biphasic illness in some cases. Further replication in other organs (depending on serotype) can be damaging to the host leading to myocarditis, hepatitis, pneumonitis and other manifestations. Enterovirus serotypes vary in their neurovirulence. CNS infection is thought to occur via haematogenous...
spread, either by direct viral penetration of the blood–brain barrier or via ‘Trojan horse’ infection of immune cells (Rhoades et al. 2011). Certainly enteroviruses tend to preferentially affect the more vascular parts of the brain, especially the brainstem. An alternate mechanism for the brainstem and anterior horn cell tropisms demonstrated by enteroviruses may be retrograde axonal transport of virus through the cranial and spinal nerves from infected muscle (Gromeier and Wimmer 1998). Once inside the CNS, enteroviruses can have a highly cytotoxic effect on host cells, inducing transcriptional shutdown and apoptosis (Rhoades et al. 2011). In addition to their direct cytotoxic effect, enteroviruses have also been reported as triggers of an ADEM presentation (Agin et al. 2010; Pillai et al. 2015).

Host factors are important in determining the severity of infection. Immunocompromised children with X-linked hypogammaglobulinaemia and T cell disorders are especially susceptible. Infants are another at-risk group; transplacental enterovirus-neutralising antibodies confer some protection to neonates encountering serotypes their mothers have previously been exposed to, but the range of circulating serotypes is large and changeable (RNA viruses demonstrate high rates of mutability and rapid antigen divergence) and maternally-derived enterovirus antibody levels fall to undetectable levels in 99% of infants by the age of 6 months (Luo et al. 2009). There have been rare cases of enterovirus encephalitis following therapeutic B-lymphocyte depletion therapy with rituximab (Quartier et al. 2003). Genetic factors may influence host susceptibility to enterovirus infection even in otherwise immunocompetent individuals. The HLA-A33 haplotype, which is more common in Asian people, confers increased susceptibility to enterovirus 71 infection (Chang et al. 2008). Enterovirus infection of the CNS occurs more often in boys than in girls.

Nonpolio enteroviruses comprise over half of all laboratory-proven viral meningitis cases in the UK (Kadambari et al. 2014). The majority of children present with self-limited meningitis only. However, in vulnerable groups (i.e. infants and the immunocompromised), enteroviruses may cause life-threatening neurological infection, and certain strains (e.g. enterovirus 71) are increasingly recognised as causes of life-threatening encephalitides even in the immunocompetent. The present section concerns those patients presenting with neurological disease other than simple meningitis, the features and management of which are discussed in the Viral Meningitis section.

Clinical features of enterovirus infections

Enteroviruses cause a wide range of non-neurological clinical manifestations including gastrointestinal and respiratory illness and nonspecific febrile illness. Several serotypes are associated with a maculopapular exanthem (e.g. echovirus 4, 9 and 16; coxsackie viruses A9 and A23) and petechial rashes have also been reported. Hand, foot, and mouth disease, outbreaks of which occur sporadically in many parts of the developed and developing world, is caused mostly by coxsackie viruses A6, A10, A16 and enterovirus 71. Several strains are associated with acute and persistent diarrhoea in young children (Rao et al. 2014). Other manifestations of enteroviral infection include haemorrhagic conjunctivitis (enterovirus 70); herpangina, parotitis (enterovirus 71, group A coxsackie viruses) and pleurodynia and myocarditis (group B coxsackie viruses). Enterovirus 68 has re-emerged as a cause of fatal paediatric respiratory infections in Asia, Europe (CDC 2011) and recently North America (Stephenson 2014). Enteroviruses are an important cause of neonatal sepsis, mostly causing a benign febrile illness, but in a proportion leading to disseminated infection and multisystem manifestations including meningoencephalitis, myocarditis, pneumonitis, hepatitis and coagulopathy (reviewed in Abzug 2014). Neonates at risk for severe disease include those with (1) onset in the first few days of life, (2) maternal illness at or before delivery, and (3) infection by echovirus 11 or coxsackie B viruses. Immunocompromised older children may present in a similar manner to neonates with disseminated multisystem infection.

Neurological manifestations of nonpolio enteroviruses include a poliomyelitis-like acute flaccid paralysis (coxsackie A4, A7, A9, A24, B5; echovirus 9, 11, 18; enterovirus 68, 70, 71, 75) (Kelly et al. 2006; Pfeiffer et al. 2015); GBS and transverse myelitis (coxsackie A9, B1, B4; echovirus 6; enterovirus 70); and cerebellar ataxia (coxsackie A4, A7, A9, B3, B4; echovirus 6, 9; enterovirus 71) (Fig. 11.13). Many serotypes – especially the coxsackie viruses and enterovirus 70, 71 and 75 – also cause meningoencephalitis, with a spectrum of disease ranging from ‘pure’ encephalitic disease to ‘pure’ meningitis. These frequently occur in outbreaks where only a small proportion of individuals have the more severe encephalitic presentation (Huang et al. 2003). Encephalitis accounts for only 3% of neurological enterovirus infections (Stahl et al. 2011) but a much larger proportion of the morbidity and mortality.

Enterovirus 70 and 71 have a particularly strong neurotropism. The latter (EV71) may present with neurological manifestations including meningoencephalitis, transverse myelitis, opsochlonus–myoclonus, cerebellitis and GBS in up to one-third of children with hand, foot and mouth disease (Tyler 2009), although most series report a neurological complication rate of 9–15% (Prager et al. 2003; Lee et al. 2013) and severe disease in less than 1% (Ho et al. 1999). Variations in neurovirulence may be due to different genetic subtypes. Since first being isolated in 1969, EV71 has steadily expanded its range (Tyler 2009) with major paediatric outbreaks in Bulgaria, Hungary, Taiwan, Japan, Korea, Singapore, Australia, Vietnam, Brunei, India, Malaysia and Cambodia (Wilson 2013; Abzug 2014). The largest known epidemics in recent years have been in China, where EV71 is the most common enterovirus serotype isolated from the stools of healthy children of anterior horn cell disease. Respiratory failure (Wu et al. 2013), and annual outbreaks caused 876 deaths from 2008 to 2010 (Tân et al. 2011). Smaller pockets of disease have occurred in North America, Western Europe and the UK (reviewed in Abzug 2014).

The most devastating manifestation of EV71 is a brainstem syndrome with high fatality characterised by rhomboencephalitis with associated cardiac failure, neurogenic pulmonary oedema and/or acute flaccid paralysis (Chen et al. 2007).
Preschool children are most commonly affected. Pathological findings are of cavitating lesions in the brainstem with direct invasion of virus. Cardiorespiratory failure is not due to direct viral invasion in most cases (Fu et al. 2004); the pathogenesis is not fully understood but is thought to result from some combination of systemic cytokine response and damage to the respiratory and vasomotor centres in the brainstem, leading to increased pulmonary permeability and systemic vasocstriction, with subsequent pulmonary oedema and left ventricular dysfunction (Solomon et al. 2010). Pulmonary complications can appear as early as day 2–3 of illness (Prager et al. 2003). The neurological features are those of a brainstem encephalitis syndrome (see Brainstem Encephalitis in the Viral Encephalitis section). Recurrent or sustained seizures are unusual and may indicate involvement of brain regions other than the brainstem, such as the hippocampus, cerebral cortex, thalamus, putamen and subcortical white matter (Lee et al. 2013).

**Diagnosis of Enterovirus Infections**

Enterovirus may be detected in a range of specimens including CSF, serum, urine, stool, vesicle fluid and swabs of the rectum, throat and nasopharynx. Detection of virus by real-time PCR is quicker and more sensitive than by culture (Abzug 2014) and can be used for strain-specific genotyping (Mirand et al. 2008). Although detection of virus in the CSF or brain is the criterion standard for diagnosis of enterovirus meningoencephalitis, the diagnostic yield may be higher from other sites including the throat, rectum and vesicles (Lee et al. 2006). If available, vesicle fluid is an especially useful sample, as it is always indicative of acute infection, unlike virus in the throat or gastrointestinal tract which may represent chronic viral carriage (Ooi et al. 2010). Serum IgM is of little value in diagnosing enterovirus encephalitis (Fowlkes et al. 2008).

In EV71 encephalitis, the CSF typically shows ten to 100 white blood cells per mm$^3$, predominantly lymphocytes, although pleocytosis may be absent. MRI typically shows characteristic T2- and FLAIR-hyperintensity in the dorsal pons and medulla, with changes also reported in the midbrain and dentate nuclei of the cerebellum (Shen et al. 1999) (Fig. 11.18). In some cases of EV71 brainstem syndrome, the neuroimaging is normal (Lee et al. 2013). Those with poliomyelitis-like acute flaccid paralysis may show anterior horn cell hyperintensity and T1 enhancement in the ventral spinal roots (Abzug 2014).

**Management of Enterovirus Infections**

In the absence of any currently approved specific antiviral therapy (Abzug 2014), the mainstay of care is supportive. Intensive care therapies are often required to manage the EV71 brainstem syndrome, with particular focus on management of cardiac and pulmonary involvement, which can progress rapidly to cardiorespiratory collapse (Prager et al. 2003). Treatment with pleconaril and IVIg has been tried in paediatric EV71 encephalitis (Nolan et al. 2003). Pleconaril is a drug that integrates into the capsid of enteroviruses, preventing the virus from attaching to cellular receptors and releasing viral RNA into the cell. There is some randomised controlled trial evidence for its efficacy in aseptic meningitis in adults (Desmond et al. 2006) but there have been no trials assessing its role in enterovirus encephalitis and it is not widely available (Kneen et al. 2012). Enteroviruses require neutralising antibodies to clear so it is reasonable to consider the use of IVIg in the moribund patient. Although there is no randomised controlled trial evidence to support this, there was a suggestion of benefit in a recent Taiwanese outbreak (Ooi et al. 2010). Clinical trials of a hyperimmune IVIg from Chinese donors with high titres of EV71 antibody are in progress (Cao et al. 2011) and several other candidate drugs have been identified for development (Abzug 2014). The success of the global poliovirus vaccination effort has prompted consideration of vaccination programmes against other enteroviruses. The large number of circulating strains presents a considerable challenge for vaccine design (Rhoades et al. 2011). Recently three candidate vaccines for enterovirus 71 have shown efficacy in phase 3 clinical trials, and two have subsequently been approved by regulatory authorities in China (reviewed in Reed and Cardosa 2016).

**Outcome of Enterovirus Infections**

Fatal enterovirus encephalitis is particularly associated with the EV71 brainstem syndrome (Fowlkes et al. 2008). Mortality is in those aged 6–12 months (Ho 2000). The majority of fatal cases are associated with left ventricular failure, pulmonary oedema or haemorrhage (Ho et al. 1999; Fu et al. 2004).

Survivors of EV71 brainstem encephalitis with cardiopulmonary failure have a high rate of sequelae including limb weakness, swallowing difficulties, developmental delay and reduced cognitive function. Children with enterovirus 71 meningoencephalitis without cardiopulmonary involvement had a much better outcome, with developmental delay in only 5% of cases (Chang et al. 2007).

Imported poliomyelitis should be considered in Western travellers returning from these regions (Stewardson et al. 2009).

Cases of paralytic poliomyelitis following immunisation with the oral live vaccine (Sabin type) have been reported in immunodeficient patients; for example, those with T cell disorders or X-linked hypogamaglobulinaemia, and in immunodeficient contacts of vaccine recipients (CDC 2012a). Such individuals may develop neurological symptoms many years after exposure due to genetic reversion of vaccine virus to neurovirulence (DeVries et al. 2011). Nonimmunocompromised children can also rarely be affected by vaccine-derived paralytic poliomyelitis and some strains with reacquired neurovirulence have the capacity to circulate and infect others. Most industrialised countries now use inactivated polio vaccine in their routine immunisation schedules to avoid the problem, termed vaccine-associated paralytic poliomyelitis (Abzug 2014).

The pathological lesions in poliomyelitis involve the anterior horn cells, the motor and sensory cranial nuclei of the medulla,
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Chapter 11

The reticular formation, the cerebellar vermis and, to a lesser extent, the thalamus and layers III and V of the motor cortex. An isolated bulbar form rarely occurs. Neurons undergo degenerative changes accompanied by an initially polymorphonuclear reaction, which later becomes mononuclear.

The clinical manifestations of poliomyelitis appear after an incubation period of 3–35 days. Initial symptoms consist of headache, vomiting and fever, followed, within 2–5 days, by signs of meningeal irritation and severe pain in the lower back and limbs. Asymmetrical flaccid paralysis appears during the first two days of the major illness and involves the legs, arms and/or trunk, with absent tendon reflexes. All cranially innervated muscles may be affected. Urinary retention is present at onset in 20–30% of cases. Sensory loss is unusual. The polioviruses have a broad range of neurotropisms (Rhoades et al. 2011) and can infect most parts of the CNS; hence, poliovirus may present with features of encephalitis in addition to those of anterior horn cell disease. Respiratory failure may be secondary to brainstem involvement or paralysis of the diaphragmatic and intercostal muscles.

Examination of the CSF typically shows 30–200 white cells per mm³. Initially, these are predominantly polymorphonuclear cells, followed after 5–7 days by a lymphocytic pleocytosis. The protein content rises late, reaching a maximum around the twenty-fifth day of illness. MRI changes in the anterior horn of the spinal cord and bilateral substantia nigra have been reported (Choudhary et al. 2010). Before clinical onset the virus can be isolated from the stools and oropharynx as early as 19 days and as late as 3 months after the first clinical features (mean 5 weeks). Typing of the virus shows one of the three types of poliovirus. Serological diagnosis is made by demonstration of an elevation of the titre of neutralising or complement-fixing antibodies.

The differential diagnosis includes GBS, although this is usually easily distinguished due to its differing pattern of onset, symmetrical distribution of weakness and CSF findings. Other enteroviruses have also been reported to cause a polio-like illness (Kelly et al. 2006). Arboviral infection with West Nile virus (see West Nile Virus section) or tick-borne encephalitis virus (see Tick-Borne Encephalitis Virus section) can also present as acute flaccid paresis. Cases of intoxication by chemicals may clinically mimic the condition (Gear 1984). Infant botulism (see Botulism section) should also be considered as a cause of acute flaccid paralysis (Kelly et al. 2006).

There are no effective antiviral treatments for poliovirus. Supportive management may include mechanical ventilation in cases of paralytic poliomyelitis with respiratory failure. The prognosis of paralytic poliomyelitis depends on the extent of involvement, with death from respiratory muscle paralysis in 5–10% (McFee 2013). Recovery in some affected muscles is observed for up to one year or more, but muscles remaining completely paralysed after one month usually remain so indefinitely. A progressive motor neuron disease (post-polio syndrome) resembling amyotrophic sclerosis is sometimes observed in adults 20 or more years after an acute attack (Dalakas et al. 1986).

Parechoviruses

Although assigned to a different genus in 1999 (formerly echovirus 22 and 23), the parechoviruses are included here due to their clinical similarity to the enteroviruses. They share with enteroviruses a faecal–oral/respiratory mode of transmission. Rates of infection vary significantly year by year; in outbreak years, parechovirus may be more common than enterovirus as a cause of CNS infection in at-risk groups such as young infants (Harvala et al. 2009). Like the enteroviruses their neurological presentation is mostly with aseptic meningitis, although encephalopathy can occur in the context of a disseminated infection. CSF pleocytosis is unusual. Three-quarters of meningitis and/or encephalitis cases occur in infants; human parechovirus type 3 is implicated in severe neonatal disease with sepsis, encephalitis and hepatitis (Harvala et al. 2010). Parechoviruses can also cause white matter injury in infants (Verboon-Maciolek et al. 2008; Gupta et al. 2010b). Parechovirus testing should be considered in all children less than 3 years of age presenting with suspected meningitis and/or encephalitis There is no specific antiviral treatment.

RESPIRATORY VIRUSES

Respiratory infections are a common antecedent to encephalitis in children. Some cases are caused by Mycoplasma pneumoniae and streptococcal species but the majority are viral infections including the influenza viruses, adenoviruses and respiratory syncytial virus (see Paramyxoviruses section for the latter). Respiratory-virus-associated encephalitis shows a predilection for the thalami and basal ganglia on neuroimaging, accounting for 44% of such findings among cases in the California Encephalitis Project (Beattie et al. 2013). Many respiratory viruses – particularly the influenza viruses – are also associated with a range of para-infectious encephalopathies (see Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses section). Encephalopathy occurring in the context of recent or concomitant respiratory tract infection should prompt PCR testing for respiratory viruses in the CSF and respiratory tract, which may include samples of the sputum, nasopharyngeal aspirates, tracheal aspirates and throat or nasal swabs as appropriate (Kneen et al. 2012). PCR detection of aerosolised respiratory viruses in air is also possible and may become more widely available in future (Perrott et al. 2009).
Influenza A and B

Influenza A and B are the main disease-causing genera of RNA virus of the family Orthomyxoviridae. Although the majority of infants and children infected with influenza have a mild respiratory illness only, more severe manifestations of disease with encephalopathy are increasingly recognised. Encephalitis with direct invasion of the CNS is unusual as influenza has no known neurotropism. More common is influenza-associated encephalopathy in the absence of detectable virus in the CSF (Stahl et al. 2011). A spectrum of specific para-infectious acute encephalopathy syndromes has now been identified (see Table 11.13 and accompanying section). These are triggered by various viral infections but are especially associated with influenza, particularly acute necrotising encephalopathy (see Acute Necrotising Encephalopathy section) (Tsai and Baker 2013; Goenka et al. 2014). Pathogenic mechanisms are not well understood but there is evidence of increased pro-inflammatory cytokines in the serum and CSF of some children with neurological manifestations of influenza, with higher levels in those with fatal outcome (Ichiyama et al. 2004; Topa et al. 2004; Hosoya et al. 2005; Nuni et al. 2005).

The encephalopathies present as acute deteriorations in consciousness in the context of influenza infection, ranging in severity from mild (febrile seizures, delirium) to devastating (coma with malignant brain oedema and haemorrhagic necrosis) (Goenka et al. 2014). Seizures occur in up to two-thirds of cases (Surana et al. 2011, Ekstrand 2012). Influenza infection precedes neurological symptom onset by 1–14 days (median 3) (Amin et al. 2008). Japanese children appear to be particularly susceptible (Sugaya 2002). The emergence of influenza A(H1N1) in 2009 heralded an increased rate of neurological complications; even outside Japan, 6–19% of children hospitalised with H1N1 suffered neurological manifestations (Ekstrand et al. 2010; Farooq et al. 2012; Khandaker et al. 2012), although this still represents only 1.2 per 100,000 infections (Glaser et al. 2012). Interestingly, a 17-fold increase in incidence of paediatric necrolysis was observed in Finland in 2010 following H1N1 pandemic vaccination in 2009 (Partinen et al. 2012). The seasonal influenza vaccine is considered safe (Tsai and Baker 2013).

A recent British population-based study reported 12 children with influenza-associated encephalopathy and 8 with encephalitis over 2 years surveillance (Goenka et al. 2014). Median age was 4 years and 28% of children had pre-existing neurological conditions. Eighty per cent of patients required admission to an intensive care unit; 84% of patients had influenza A in their respiratory secretions, of which 95% was the H1N1 subtype. CSF pleocytosis was observed in three patients only. Two-thirds of patients had abnormal EEGs. Neuroimaging was diagnostic of a specific acute encephalopathy syndrome in five children and nonspecifically abnormal in a further five.

Initial investigation is as for any acute encephalopathy (Table 11.8). Virological diagnosis is based on virus isolation or antigen detection from respiratory secretions, or seroconversion (Studahl 2003). Laboratory investigations should also include coagulation, hepatic and renal profile, with a low threshold for metabolic screening including serum ammonia, and urine amino- and organic acids. T1, T2 and diffusion-weighted magnetic resonance sequences are recommended for identification of acute encephalopathy syndromes with specific clinical and prognostic implications (see Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses section). Recurrent or familial cases of AEN should be tested for RANBP2 mutations (see Acute Necrotising Encephalopathy section) (Singh et al. 2015).

In the absence of any proven specific therapies (Goenka et al. 2014), management of influenza-associated encephalopathy is largely supportive, although treatment with the neuraminidase inhibitor oseltamivir may be helpful if started promptly in H1N1 infection (within 48–72 hours of symptom onset) (Straumanis et al. 2002; Crawford 2010). CSF penetration is poor but severity of systemic disease may be reduced. Oseltamivir-resistant H1N1 may be treated with zanamivir (van der Vries et al. 2010). Early administration of steroids may be beneficial in AEN (Okumura et al. 2009). IVlg is sometimes given in the severely unwell but the benefits have not been proven. Plasma exchange (Kawashima et al. 2005) and therapeutic hypothermia (Yokota et al. 2000) have also been tried. Overall outcome in the British series of influenza-associated encephalitis and encephalopathy was poor in two-thirds, including death in 16% of cases (Goenka et al. 2014). A smaller European series reported full recovery in two of five cases (Surana et al. 2011).

Adenoviruses

The genus Mastadenovirus (family Adenoviridae) includes more than 50 serotypes of double-stranded DNA virus known to cause disease in humans, ranging from mild respiratory, gastrointestinal, pharyngo-conjunctival and urinary tract infections to hepatitis, pancreatitis, nephritis, myocarditis and disseminated infection with multi-organ failure (Goncalves and de Vries 2006; Lynch et al. 2011). They are included in this section as respiratory viruses as this is the most common presentation in children. CNS manifestations of adenovirus infection also vary widely and include aseptic meningitis (de Ory et al. 2013), myelitis, subacute focal encephalitis, and acute encephalopathy syndromes ranging from transient and mild (Strausberg et al. 2001) – for example, clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) (see Clinically Mild Encephalitis/Encephalopathy with Reversible Splenial Lesion section) (Takanashi 2009) – to severe, including Reye syndrome and haemorrhagic shock and encephalopathy syndrome (HSES) (see Haemorrhagic Shock and Encephalopathy Syndrome section) (Gefen et al. 2008). CNS involvement is relatively rare in immunocompetent children. Serotypes vary in their neurotropism. CNS involvement is more commonly reported with serogroup B1, followed by serogroup A and serogroup C (Reyes-Andrade et al. 2014). Serotype 7 is associated with meningoencephalitis with a rather severe course.
Most children with CNS involvement are younger than 5 years and present with co-existing respiratory symptoms (Reyes-Andrade et al. 2014). Severe adenovirus infection in the immunocompetent may mimic bacterial sepsis with significantly elevated acute phase reactants (Chuang et al. 2003) and petechial rash (Schneider et al. 2013). Neurological features are highly variable but may include seizures, encephalopathy, irritability, psychosis and hallucinations, meningsis and weakness. Cerebral infarction is reported in some cases. Diagnosis is most commonly by detection of virus in samples from the nasopharynx, throat, sputum or stool. Viral detection by CSF PCR is diagnostic of meningoencephalitis and absent in para-infectious encephalopathies.

Management is largely supportive in immunocompetent children. Children with disseminated infection should be evaluated for immunocompromise and considered for treatment with cidofovir or ribavirin (Lynch et al. 2011; Reyes-Andrade et al. 2014). Novel therapeutic options include CMX001 (T ebruegge and Curtis 2012) and administration of antigen-specific cytotoxic T lymphocytes (Leen et al. 2009). CNS manifestations of adenovirus are often reversible and follow a benign course (Straussberg et al. 2001). One series reported full recovery in 91% of cases (Huang et al. 2013). However, some cases are associated with permanent sequelae (Chuang et al. 2003), especially HSES (Gefen et al. 2008).

**Respiratory Syncytial Virus**

Respiratory syncytial virus (RSV) is a common cause of seasonal respiratory tract infection in infants and is associated with apnoea in up to 21% of cases, particularly in younger infants, which may be of central origin (Kneyber et al. 1998). Older children may present with febrile convulsions (Millichap and Millichap 2006). Encephalopathy has been reported in 0.3–1.8% of cases (Ng et al. 2001; Sweetman et al. 2005; Millichap and Wainwright 2009) although encephalitis is rare (Hirayama et al. 1999). Rates of neurological complications in children admitted to intensive care units with respiratory syncytial virus may be as high as 36.4% (Kho et al. 2004) and largely relate to hypoxia-ischaemic events and requirement for extracorporeal membrane oxygenation (Millichap and Wainwright 2009). EEG abnormalities are common and focal neurological deficits are also reported. Long-term sequelae occurred in 37% of cases in one intensive care unit series of respiratory syncytial virus with neurological manifestations (Millichap and Wainwright 2009).

**ARBOVIRUSES**

The arboviruses (arthropod-borne viruses) are the most important causes of encephalitis globally. The group is defined by the vector-borne mode of transmission (via mosquito, tick or sandfly bite) rather than by taxonomy, although all but one are RNA viruses belonging to one of four families: Flaviviridae, Togaviridae, Bunyaviridae and Reoviridae. Most are transmitted from vertebrate animals to humans (zoonotic), with bird or mammal reservoirs acting as amplifying hosts and humans usually dead-end hosts (Stahl et al. 2011). Dengue and Chikungunya are exceptions in which humans are the principal reservoir host. Seasonality of arboviral infection in endemic areas varies by vector and region; in addition, epidemics of infection across a larger geographical area may lead to significant year-to-year variations in incidence. Infection with arboviruses is usually asymptomatic or results in mild non-specific disease only; neurological manifestations occur even less commonly, ranging from aseptic meningitis and transient encephalopathy to severe and sometimes fatal encephalitis. For all arboviruses the presumed route of entry to the CNS is via penetration of the BBB. This is supported by an established predilection for the midbrain, thalamus and basal ganglia (suggesting haematogenous spread) (Beattie et al. 2013; Wilson 2013). Diagnosis of arboviral infection is more often achieved by detection of virus-specific IgM in serum or CSF rather than by PCR (Gaensbauer et al. 2014). Cross-reactivity between viruses is common and species-specific viral-neutralisation assays – that is, demonstrating the biological activity of patient-derived antibodies to reduce viral infectivity – are usually required to confirm the diagnosis, especially for flaviviruses (Stahl et al. 2011). Acute and convalescent blood samples are recommended in all cases of suspected arboviral infection (Kneen et al. 2012). There are no effective specific treatments currently available for any of the arboviral infections. Management is, therefore, supportive.

**Arboviruses as Emerging Infections**

Arboviruses have a strong propensity to become emerging infections, that is, infections which acquire new hosts, spread into new territories, alter characteristics of their pathogenesis, or are caused by agents not previously recognised as pathogenic (Tyler 2009). Eighty per cent of emergent viruses are zoonotic and 40% of these are arboviruses (Taylor et al. 2001). Factors promoting the emergence of arboviruses include intensification of agriculture, close contact between animals and humans, and increasing population density (Tyler 2009). Novel viral infections are most likely to arise in Africa, Latin America and Asia (Jones et al. 2008). But the rapid spread of West Nile virus (WNV) across North America in 2002–3 (reviewed in Tyler 2009), and to a lesser extent the spread of Toscana virus in Europe, demonstrate the capacity for arboviruses to expand into new territories even in the West if amplifying hosts and vectors are available. Japanese encephalitis virus, tick-borne encephalitis virus, dengue and Chikungunya have also all re-emerged to some extent in recent years. Climate change, which has a major impact on the geographic range of arthropods, may push emerging arbovirus infections further into northerly latitudes in future (Patz et al. 2005). Up-to-date knowledge of local epidemiology and outbreaks is, therefore, essential for early identification of arbovirus infection, which may be easily missed in the UK and other countries where disease is not endemic. ArboZoonet is an EU-based international collaborative network that
has been established to help monitor and control emerging arboviruses in future (Ahmed et al. 2009).

**FLAVIVIRUSES**

**Japanese Encephalitis Virus**

Japanese encephalitis virus (JEV) is the most common single cause of viral encephalitis worldwide, with at least 68,000 cases per year (Campbell et al. 2011) and some 15,000 deaths (Erlanger et al. 2009), mostly in children. The natural cycle of JEV has water birds as the principal host and *Culex* spp. (Erlanger et al. 2009), mostly in children. The natural cycle of JEV has water birds as the principal host and *Culex* spp. (Erlanger et al. 2009), mostly in children. In endemic areas, exposure of humans is ubiquitous by early adulthood, but only one in 300 exposures are symptomatic.

**Pathophysiology of JEV**

After the bite of an infected mosquito the incubation period is 6–16 days, during which time the virus amplifies peripherally in the skin and regional lymph nodes. Primary viraemia leads to seeding in extraneural tissues (muscle, lymphoreticular, endocrine, exocrine) and, in less than 1% of cases (Campbell et al. 2011), penetration of the CNS by haematogenous spread, involving especially the more vascular parts of the brain (thalam, basal ganglia and brainstem). Autopsy reveals an inflammatory response to widespread neuronal infection, predominantly affecting the grey matter, with foci of haemorrhage (Tiwari et al. 2012). Susceptibility factors for CNS involvement in JEV infection are not well understood but may include reduced blood–brain barrier integrity, for example, due to neurocysticercosis (Solomon et al. 2000a). Elevated CSF levels of pro-inflammatory cytokines and chemokines are associated with poor outcome; the extent to which the host immune response is directly pathogenic is not well understood (Winter et al. 2004).

**Epidemiology of JEV**

JEV has expanded its range west across the Indian subcontinent and south into Papua New Guinea and Northern Australia in recent decades. Nearly half the world’s population now lives in the region where JEV occurs (Erlanger et al. 2009), which is approximately bound by eastern Russia in the north, Australia in the south and Pakistan in the west (Stahl et al. 2011). Around half the total number of cases currently occur in China (Campbell et al. 2011) where the incidence is falling, but incidence is increasing elsewhere including Bangladesh, Northern India, Nepal and Vietnam (Jmor et al. 2008; Tiwari et al. 2012). Infection is endemic throughout the year in the tropical regions with summer epidemics further north. Most acute infections occur in the nonimmune (younger children or recent immigrants) with peak incidence at ages 3–6 years (Tiwari et al. 2012). Areas of rice cultivation and pig farming are high risk; intensification of agriculture is expected to contribute to increased transmission in a number of resource-limited Asian countries in future, including Cambodia, Laos, Burma and North Korea (Erlanger et al. 2009). Bird migration, irrigation projects, global warming and animal smuggling may also contribute toward future geographical expansion of JEV (Tiwari et al. 2012). Mass vaccination has proven highly effective at reducing disease incidence in Japan, Korea, Taiwan and Thailand; cost and competing healthcare priorities limit vaccination availability in poorer Asian countries, despite the strong case that has been made for the expansion of such programmes (Solomon 2006).

**Clinical features**

Symptomatic infections follow a series of clinical stages. A febrile prodrome of 2–3 days with headache (70%), abdominal pain and vomiting is succeeded by an encephalitic phase (5–7 days) with seizures (80%) and coma (80%) (Ooi et al. 2008); this is followed by a subacute phase (10–12 days) with dystonia (43%) and movement disorders including parkinsonism (45%) (Kumar et al. 2006; Basumatary et al. 2013). The final phase of gradual convalescence in survivors can take weeks to months. Other presentations include focal limb weakness (25%), cranial nerve palsies, status epilepticus and a poliomylitis-like acute flaccid paralysis (Solomon et al. 1998; Gould and Solomon 2008). Older children may present with abnormal behaviour leading to misdiagnosis of primary psychiatric illness (Gould and Solomon 2008). Japanese encephalitis is more severe in younger children. Fatality peaks in the encephalitic phase and is associated with prolonged coma, status epilepticus and cerebral and/or pulmonary oedema (Tiwari et al. 2012).

**Diagnosis of JEV**

JEV may be isolated by viral culture of the peripheral blood in the first week of symptoms, although the relatively low viraemia limits sensitivity. In practice, diagnosis is more often achieved by detection of IgM in the serum and/or CSF. Presence of specific IgM in the CSF, and/or detection of virus by CSF PCR, is regarded as diagnostic. CSF rapid antigen detection using reverse passive haemagglutination, immunofluorescence and staphylococcal coagglutination is also available for both CSF and serum (Tiwari et al. 2012). CSF pleocytosis is observed in up to 82% of cases (Basumatary et al. 2013).

Brain MRI is abnormal in 90% of cases (Kastrup et al. 2008), bithalamic oedema with or without haemorrhage being the most common abnormality in children (Dung et al. 2009) (Fig. 11.19). Abnormalities may also be observed in the basal ganglia, brainstem, hippocampi, cerebral cortex and white matter (Nickerson et al. 2012). Atypical imaging findings may overlap with those of herpes simplex encephalitis (Basumatary et al. 2013).

**Management and outcome of JEV**

In the absence of any currently available curative treatments, management is focused on supportive care. Randomised
controlled trial of interferon alfa-2a in children with Japanese encephalitis failed to demonstrate improvement in outcome (Solomon et al. 2003), and nor is there any convincing evidence to support the use of ribavirin or dithiol. Trials of IVIg are in progress. Vaccination is effective in preventing the disease but availability in many affected countries is limited. Japanese encephalitis confers high mortality with rates of 20–30% (Solomon 2006; Campbell et al. 2011). Up to half of survivors suffer severe neuropsychiatric sequelae (Kumar et al. 2006) including seizures, tremors, ataxia and paralysis, or more subtle sequelae such as learning difficulties and behavioural problems (Lam et al. 2005).

**Dengue**

The four dengue virus subtypes are spread by the *Aedes aegypti* mosquito in tropical and subtropical regions worldwide. Dengue is unusual among flaviviruses in that humans are the principal vertebrate host. Infection is symptomatic in around a quarter of cases, causing fever, arthralgia and rash, with neurological involvement in 1–5% and encephalitis in less than 1% of symptomatic cases. A 30-fold increase in incidence over the past 50 years has led the WHO to declare it the world’s fastest growing vector-borne disease and warn of its pandemic potential (WHO 2012b).

**Pathophysiology of Dengue Encephalopathy**

Encephalopathy occurring in association with dengue can be caused by complications of systemic infection including shock; metabolic derangements such as hyponatraemia; hepatic failure; and intracranial haemorrhage (Carod-Artal et al. 2013). However in recent years evidence of direct neurotropism has accumulated. Dengue virus was isolated from the CSF in half of those with systemic dengue infection in one series (Araujo et al. 2012). Virus has been repeatedly isolated from brain tissue in fatal cases (Carod-Artal et al. 2013). Sequential infection with different serotypes increases the risk of severe disease.

**Epidemiology of Dengue**

Increasing urbanisation, international travel and climate change have led to the emergence or re-emergence of dengue across Asia and the Americas in recent decades. It is now endemic to over 125 countries with epidemics reported in Australia and North America (Misra et al. 2006); 96 million symptomatic infections occur annually, with the greatest numbers in the Indian subcontinent, Indonesia, Burma, Nigeria, China and Brazil (Bhatt et al. 2013). The rate of neuroinvasive disease may be increasing in recent years.

**Clinical Features of Dengue**

In younger children dengue can produce an undifferentiated fever, but in older children and adults the typical dengue fever is accompanied by arthralgia and rash. Retro-orbital headache and phobia may also occur. Symptoms usually last 2–7 days following an incubation period of 4–10 days; 1–10% of patients develop haemorrhagic fever with petechiae, gastrointestinal and gum bleeding, thrombocytopenia and increased vascular permeability. In dengue shock syndrome leads to circulatory failure.

CNS complications of dengue include dengue encephalopathy, encephalitis, and immune-mediated phenomena. Neurological features may be observed in as many as 21% of cases but most paediatric series report neurological manifestations in 0.5–5.4% (Solomon et al. 2000b; Cam et al. 2001; Panchareon and Thisyakorn 2001). Impairment of consciousness...
is the most common neurological manifestation and is probably more often caused by complications of systemic infection than by encephalitis. Other manifestations include headache, dizziness, disorientation, seizures and behavioural symptoms (Carod-Artal et al. 2013). Intracranial haemorrhage may occur in dengue haemorrhagic fever. Less common presentations include a fully reversible acute flaccid quadriparesis due to hypokalaemia (Gupta et al. 2011), and ischaemic stroke caused by cerebral vasculitis (Nanda et al. 2014). Dengue has also been linked to a range of post-infectious immune-mediated illnesses including transverse myelitis, acute disseminated encephalomyelitis, GBS and various mononeuropathies. Neuromuscular and neuro-ophthalmic complications also occur (Carod-Artal et al. 2013).

**Diagnosis of dengue**

Diagnosis of dengue fever can be confirmed by viral isolation (viral nucleic acid by PCR or viral proteins (NS1 antigen)) from peripheral blood in the first few days of illness or by elevated IgM thereafter. Definite categorisation into dengue encephalopathy or encephalitis is often challenging. The combination of pleocytosis and detectable virus in the CSF (by RNA, IgM or antigen detection) is helpful for diagnosis of the latter, although normal CSF cellularity does not exclude dengue encephalitis and the sensitivity of viral detection in the CSF is low (Carod-Artal et al. 2013). The presence of causative systemic complications is helpful for diagnosis of dengue encephalopathy. Neuroimaging in dengue may show cerebral oedema, but there are no specific neuroimaging features for dengue encephalitis and imaging is of limited use in diagnosis (Nickerson et al. 2012). EEG abnormalities (typically slowing) are present in up to half of patients with neurological symptoms (Kalita and Misra 2006) but these also do not discriminate between encephalopathy and encephalitis.

**Management and outcome of dengue**

There are as yet no effective antiviral therapies for treatment of dengue infection and management remains supportive. Patients with neurological involvement should be carefully assessed for correctable complications of systemic illness. At least six candidate vaccines are currently in clinical development and the Dengue Vaccine Initiative is coordinating efforts in developing countries. The outcome of dengue encephalopathy depends on the cause. The outcome of dengue encephalitis is variable but can be fatal.

**West Nile Virus**

West Nile virus (WNV) is another mosquito-borne flavivirus which has expanded its range in recent years, notably spreading across North America since 1999. Birds are the amplifying vertebrate host and *Culex* spp. mosquitoes are the principal vectors (Tyler 2009). Transmission has also been reported from organ donation (Iwamoto et al. 2003) and transplacentally (CDC 2002). Around 80% of infections are asymptomatic, 20% cause a nonspecific flu-like illness only, and less than 1% lead to neuroinvasive disease (Tyler 2009).

**Pathophysiology of WNV**

Animal models suggest haematogenous spread across the blood–brain barrier is the most likely route of entry to the CNS (Xiao et al. 2001). The mechanisms of CNS invasion in humans are incompletely understood. It is known that host genetic factors contribute to the risk of developing neuroinvasive disease (Glass et al. 2006). Direct viral invasion of neurons leads to damage by a combination of viral-mediated and immune-mediated mechanisms (Smith et al. 2014).

**Epidemiology of WNV**

WNV caused relatively mild outbreaks of febrile illness in Africa, the Middle East and Asia until the mid-1990s, when more severe outbreaks with higher rates of neuroinvasion began to occur in the Middle East and Eastern Europe (Smith et al. 2014). The virus first arrived in North America in 1999 and from New York spread rapidly across the continent in 2002–3. It has since spread to Latin America and the Caribbean. The virus is now considered endemic in the United States (Stahl et al. 2011); 5674 cases were reported in 2012, the highest since 2003 (Wilson 2013). Younger children are less likely to suffer symptomatic WNV infection than teenagers and adults, and the rate of neuroinvasive disease is also lower in children, although at least 505 paediatric cases occurred in the United States between 2003 and 2012 (Gaensbauer et al. 2014). Peak age of incidence for neuroinvasive WNV in children is 15–17 years. Incidence is highest in the North Central and Mountain regions. Smaller outbreaks continue to occur in Southern Europe including Romania, Bulgaria, Italy, France and Greece.

**Clinical features of WNV**

After an incubation period of 2–15 days WNV causes a nonspecific illness lasting 3–7 days characterised by high fever, headache, myalgia and fatigue (Smith et al. 2014). Vomiting and diarrhoea are prominent in around a quarter of patients. Physical examination may reveal a macular rash and lymphadenopathy. Fatigue can persist for several months.

Neuroinvasive WNV can cause the full spectrum of meningoencephalitis from pure encephalitis to pure meningitis. Onset of neurological symptoms may be during the febrile phase or delayed. Meningitis is the more common presentation in children and produces the usual symptoms of aseptic meningitis (see Viral Meningitis section) in addition to cranial nerve palsies (particularly the facial nerve) in around 20% of cases (Tyler 2009). WNV encephalitis is more serious, characterised by the usual fever, headache and encephalopathy, plus a range of movement disorders including myoclonus, tremor, parkinsonism and ataxia (Tyler 2009). Seizures are rare (Smith et al. 2014).

A poliomyelitis-like acute flaccid paralysis is also observed in 5–10% of patients with neuroinvasive disease (Sejvar et al. 2014).
Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus (TBEV) is endemic across much of Eastern Europe and Russia with a range extending from eastern France to Siberia and Japan. There are three main subtypes, all of which circulate in Europe, although the most severe strain occurs mainly in East Asia. The vectors of TBEV are ticks of the *Ixodes* genus. Humans are accidental hosts; rodents are the natural reservoir. Humans can also be infected by consumption of unpasteurised dairy products although this mode of transmission is not reported to cause encephalitis (Stahl et al. 2011). As with most arboviruses, the majority (70–95%) of infections are asymptomatic (Gritsun et al. 2003).

Pathophysiology of TBEV

The virus is transmitted from the salivary glands of the tick to the skin during the first few minutes of a blood meal. Initial replication occurs in the subcutaneous tissue and regional lymph nodes. Further replication occurs within circulating leukocytes during viraemia and the virus seeds numerous extraneural sites. CNS invasion occurs during viraemia via incompletely understood vascular mechanisms (Ruzeck et al. 2010). Within the CNS, neuronal infection by TBEV induces an inflammatory reaction involving cytotoxic T cells (Gelpi et al. 2006) in which tissue and meningeal infiltration, peri-vascular cuffing, and (less commonly) infiltration of the nerve roots are observed (Jellinger 1981). Tissue necrosis occurs in affected areas in fatal cases.

Epidemiology of TBEV

In some regions of Russia, Latvia, Lithuania and Estonia, TBEV is the most common infection of the CNS, with incidence as high as 51 per 100,000 (Centre for Communicable Diseases and AIDS 2010). TBE also occurs in Germany, Austria, Czech Republic, Poland, Switzerland, Slovakia and Hungary (Kollaritsch et al. 2011). The ticks live in the moist undergrowth of forest floors and feed during spring and summer; hence, childhood presentation with TBE is more common during the summer months. The number of cases in Europe has increased by 400% in recent decades due to climate change and other factors (Suss 2008); around 2500 cases of TBE are recorded annually across the continent.

Clinical features of TBEV

TBEV in children is generally milder than in adults, although severe illness can occur, especially in vulnerable groups such as young infants (Leistner and Dahlem 2011). Less than half of cases present with a clear history of a preceding tick bite. An incubation period of 3 days to 3 weeks precedes onset of non-specific flu-like symptoms including fever, myalgia, arthralgia and headache. After up to a week of symptoms most patients then make a full recovery; however, 20–30% have a biphasic course with recurrence of fever after 2–10 days accompanied by neurological symptoms (Dumps et al. 1999). Neurological disease is usually restricted to aseptic meningitis but encephalitis...
occurs in around one-third of children. The virus has a cerebellar tropism; ataxia is commonly seen in both the meningitic and meningoencephalitic presentations. Cerebral cortical involvement is usually restricted to the motor areas. Myelitis and meningoaraculoneuritis are also reported, presenting with, for example, flaccid paresis of one or more limbs (classically upper). The more severe strains may have slower onset of neurological symptoms (Gould and Solomon 2008). Marked lethargy and sleepiness are described during recovery (Ruzek et al. 2010).

**Diagnosis of TBEV**

Diagnosis is by demonstration of anti-TBEV IgM in the CSF and/or serum, four-fold elevation in IgG across paired samples, or direct viral detection by PCR (Kollaritsch et al. 2011). The differential diagnosis of neurological symptoms following a tick bite in Europe includes ehrlichiosis and Lyme borreliosis (Cizman et al. 2000).

**Management and outcome of TBEV**

There is no specific treatment for TBEV (Ruzek et al. 2010). TBEV is a vaccine-preventable disease and immunisation should be offered to all children living in or travelling to endemic areas. Post-exposure immunisation is not capable of producing effective concentrations of neutralising antibodies and is not recommended, although completion of an incomplete course started prior to exposure may be considered (Broker and Kollaritsch 2008). Mortality is reported as 1–2% for the Western subtype but may be as high as 40% for the Far Eastern subtype (Mansfield et al. 2009). Persistent epilepsy, weakness and/or neuropsychiatric sequelae occur in around 10% of children affected by European strains (Haglund and Gunther 2003) and up to 60% of survivors of Far Eastern strains (Gould and Solomon 2008). Persisting neurological signs may represent chronic infection.

**Other Flaviviruses**

*St Louis encephalitis* virus is related to JEV and WNV but is only found in the Americas. Around 50 cases are reported annually in North America although epidemics affecting up to 800 per 100,000 people arise every 5–15 years (Gould and Solomon 2008). From 2003 to 2012 there were only four reported paediatric cases in the United States (Gaensbauer et al. 2014). *Culex* spp. mosquitoes are the vectors and birds are the reservoir host. The flu-like illness may be complicated by meningoencephalitis or encephalitis. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is reported to occur in one-third of cases (Stahl et al. 2011). Mortality is less than 10%.

Powassan virus also causes CNS infection in North America where it is the only tick-borne flavivirus cause of encephalitis. It is closely related to the severe strains of TBEV that occur in eastern Russia. It is exceptionally rare with only eight reported paediatric neuroinvasive cases in the United States from 2003 to 2012 (Gaensbauer et al. 2014) but has a high fatality rate with severe sequelae in survivors (Stahl et al. 2011).

Louping ill virus is a UK relative of TBEV found in ticks of the Irish, Scottish, Welsh and English moorlands (Gould and Solomon 2008). It causes encephalomyelitis in sheep and very rarely in humans with one documented fatality (Davidson et al. 1991). Local TBEV lineages also occur rarely in forested regions of Spain, Norway, Turkey, Greece, Siberia and India (Gould and Solomon 2008).

Murray Valley encephalitis virus is transmitted by mosquitoes in Australia and New Guinea. It rarely produces a similar illness to JEV with mortality of up to 30% (MacKenzie 2005).

Zika virus, first documented in Uganda in 1947, was regarded as a relatively unimportant pathogen for many years. However, from 2007 it increased its geographical range to 52 new countries (Brouet et al. 2016) and became the focus of global media attention in 2015 when it was linked to a marked increase in congenital microcephaly in Brazil. The putative link between prenatal Zika virus infection and congenital brain anomalies (reviewed in Rasmussen et al. 2016; de Fatima Vasco Aragao et al. 2016) is beyond the scope of this chapter. Postnatally, Zika is transmitted to humans by mosquitoes mainly of the genus *Aedes*, or by human sexual contact. Symptoms are usually mild and nonspecific, including fever, rash, conjunctivitis, myalgia, malaise and headache, lasting for 2–7 days. The virus is neurotropic in animal models but its link to neurological disorders in humans remains controversial (Brouet et al. 2016). A case-control study of 42 adults presenting with GBS during a 2013–14 Zika outbreak in French Polynesia found serological evidence of Zika infection in all GBS cases versus 56% of controls, and evidence of recent infection (positive anti-Zika IgM) in 93% of cases versus 17% of controls. At population level, the peak incidence of GBS was found to follow the peak incidence of Zika by an interval of around 3 weeks (Cao-Lormeau et al. 2016). All other literature linking postnatally acquired Zika to neurological disorders is based on individual cases. Zika virus was detected by PCR in the CSF of a 15-year-old girl with acute hemiparesis and lesions in the cerebral and thoracic cord on MRI. She was given a short course of intravenous methylprednisolone and had reasonable recovery of neurological function (Mécharles et al. 2016). A case of meningoencephalitis associated with Zika infection was described in an 81-year-old man (Carteaux et al. 2016). Our understanding of Zika-associated neurological disease is expected to be refined in future following the WHO’s declaration of a Public Health Emergency of International Concern in February 2016.

**Togaviridae**

All togaviridae causing disease in humans are found in the genus *Alphavirus*.

*Eastern equine encephalitis virus* (EEEV) is the most neurovirulent of these. It is widespread in the eastern parts of Central and South America and is also found along the Atlantic and Gulf coasts of North America. Birds are the reservoir host in North America, while rodents and marsupials are the reservoir...
in South America (Stahl et al. 2011). Throughout the Americas, mosquitoes are the vectors and both humans and horses are dead-end hosts. Most infections are asymptomatic but encephalitis caused by EEEV can be severe. In the United States it occurred at least 30 paediatric encephalitis cases from 2003 to 2012, half of which occurred in children younger than 4 years (Gaensbauer et al. 2014). 90% of cases occurred in summer. Case fatality rate was 33% and disabling sequelae are reported in survivors.

Western equine encephalitis virus is a similar agent affecting the western half of the Americas. It previously caused more cases of encephalitis than EEEV (Arpino et al. 2009) but appears to have declined in recent years (Stahl et al. 2011) and is less neurovirulent with a fatality rate of 3–10%.

Venezuelan equine encephalitis virus is the third major alphavirus of the Americas. It is the least neurovirulent but is re-emerging in Brazil and other South American countries (Stahl et al. 2011). Rodents are the reservoir and new strains emerge frequently as large outbreaks in horses and humans, transmitted by various vectors (Powers et al. 1997).

Chikungunya is a mosquito-borne alphavirus endemic to sub-Saharan Africa and tropical Asia. Humans and other primates are the vertebrate reservoir host. A major re-emergence in 2004 began in Kenya and spread rapidly around the Indian Ocean to infect some 6 million people (reviewed in Das et al. 2010). The virus is now endemic in the Indian subcontinent (Pialoux et al. 2007). Cases have subsequently been exported to the UK and mainland Europe (Das et al. 2010) including a small outbreak in northern Italy (Rezza et al. 2007). Unusually for an arbovirus, infection results in symptomatic illness in more than 85% of cases (Stahl et al. 2011), with fever, rash, myalgia, headache, photophobia and a distinctively severe arthralgia. The fever is described as subsiding and recurring in a ‘saddleback’ pattern similar to dengue (Rajapakse et al. 2010). Fever resolves over weeks but arthralgia can persist for many months. Neurological manifestations, occurring in up to 61% of children aged more than 3 years (less in younger children) (Ernould et al. 2008), include acute encephalopathy, meningism, seizures, encephalitis and GBS (Wielanek et al. 2007; Robin et al. 2008). Excepting GBS, neurological manifestations begin in the first few days of illness, and CSF is usually unremarkable (Arpino et al. 2009). Diagnosis is by PCR identification of virus, elevated IgM or rising IgG. CNS co-infection has been described, particularly with dengue. CT and MRI are usually normal but may show generalised cerebral oedema; haemorrhages, white matter changes and ring-enhancing lesions have also been described (Rajapakse et al. 2010). EEG is usually abnormal in children, demonstrating frontal slowing, burst-suppression and paroxysmal polyspikes (Robin et al. 2008). Long-term sequelae including cognitive impairment and disorders of behaviour and communication occur in 10–25% of cases (Robin et al. 2008; Lewintraube et al. 2009). Death can occur, particularly in haemorrhagic cases, and in neonates affected by vertical transmission.

**BUNYAVIRIDAE**

La Crosse virus (LACV) is the most common neuroinvasive arboviral infection of children in North America with at least 665 cases from 2003 to 2012 – more than WNV (Gaensbauer et al. 2014). It is transmitted by the *Aedes triseriatus* mosquito; squirrels and chipmunks are amplifying hosts. Peak age of incidence is 5–9 years. Most infections occur in summer in forested areas of the Midwest and Appalachian regions. 78% of children present with encephalitis, 20% with meningitis and 2% with acute flaccid paralysis. The encephalitis has a mortality around 1% and results in epilepsy in some survivors. Related viruses to La Crosse virus include Jamestown Canyon and California encephalitis virus in the United States and Tähyna virus in Europe (Stahl et al. 2011).

The most important Bunyavirus in Europe is the Toscana virus, first isolated in 1971 (Tyler 2009). Sandflies are the vectors and possibly also the reservoir host (Stahl et al. 2011). Infections occur in Spain, Portugal, France and especially central Italy, where it is the most common cause of viral meningitis in the summer months (Charrel et al. 2005). Most infections cause a mild febrile illness only but the virus also has a neurotropism, causing mostly meningitis with associated tremors and myalgia (Tyler 2009). CSF typically shows a lymphocytic pleocytosis with elevated protein and normal glucose (di Nicuolo et al. 2005). Encephalitis is rare and most patients make a full recovery. Related viruses to Toscana in Europe include the Sicilian and Naples viruses (Stahl et al. 2011).

**REOVIRIDAE**

The family *Reoviridae* includes coltiviruses and seadornaviruses. The most important of the former is Colorado tick fever virus, which is transmitted by high altitude ticks in North America. Squirrels and chipmunks are the reservoir hosts. Cases in humans occur in summer and cause encephalitis in 5–10% of symptomatic infections (more in children). Eyach virus is a related coltivirus implicated in similar presentations in France and Germany. The only important seadornavirus in humans is Banna virus, which is transmitted by mosquitoes in Southeast Asia. It is reported to cause encephalitis and may be misdiagnosed as JEV (Attoui et al. 2005).

**PARAMYXOVIRUSES**

Several single-stranded RNA viruses of the family *paramyxovi-ridae* are associated with acute CNS disease in children.

**Measles Virus**

Primary infection with measles causes respiratory tract infection and the characteristic exanthem. The virus spreads by aerosolised droplets and is highly contagious. It causes over 145 000 deaths globally per year (Perry et al. 2014), largely due to pneumonia. There has been an increase in measles cases
Acute primary measles encephalitis

From the epithelial cells of the respiratory tract the virus spreads to local lymph nodes where secondary replication occurs, followed by invasion of the blood and other organs. Slight pleocytosis is sometimes observed during primary infection in the absence of neurological signs or symptoms. 1–3 per 1000 cases are complicated by direct CNS invasion of virus, i.e., primary encephalitis (Hosoya 2006). This typically occurs during the exanthematous stage of infection, although in some cases rash follows neurological involvement (Johnson et al. 1984), or does not occur at all (Wairagkar et al. 2001), especially in children with T cell immunodeficiencies (Sabellà 2010). Neurological features include headache, encephalopathy, seizures, ataxia and weakness (Buchanan and Bonthius 2012). CSF analysis reveals marked lymphocytic pleocytosis with mild elevation of protein. PCR detection of measles virus in the CSF is diagnostic of primary meningoencephalitis. Detection of measles virus in urine by culture or PCR may be supportive in the absence of positive CSF (Kneen et al. 2012). MRI reveals focal hyperintensities on T2-weighted imaging. EEG may show diffuse slowing and focal or generalised epileptiform discharges. Raised intracranial pressure may occur as a result of brain oedema and lead to secondary brain injury (Bonthius and Karacay 2002). Treatment is supportive in the absence of any proven antiviral treatment, although ribavirin in effective against measles virus in vitro (Buchanan and Bonthius 2012). The course is often severe and may be fatal in up to 10–15% of cases (Perry and Halsey 2004). Learning difficulties, seizures and behavioural disturbances are common in survivors.

Acute disseminated measles encephalomyelitis

Measles also causes post-infectious acute disseminated encephalomyelitis (ADEM) in 1 per 1000 cases, making it one of the most common causes of ADEM worldwide (Chowdhary et al. 2009; Reuter and Schneider-Schaullies 2010). Presentation is during the resolution phase or several weeks later (Buchanan and Bonthius 2012). Virus is not detected in the CSF. Clinical features and management of ADEM are discussed in Chapter 12. Outcome of measles-associated ADEM is better than for primary measles encephalitis. ADEM is also described following measles immunisation, albeit extremely rarely (one to two per million vaccinations) and usually in a milder presentation (Tenembaum et al. 2007).

Mumps Virus

Mumps virus is transmitted by inhalation of, or oral contact with, aerosolised droplets. Its principal primary manifestation is parotitis; it also causes orchitis and pancreatitis. Around one-third of infections are asymptomatic (Philip et al. 1959). The virus is highly neurotropic, accessing the CNS via the choroid plexus or transiting mononuclear cells (Rubin et al. 2015). CNS infection is the most common extrasalivary-gland manifestation of mumps (Hvidt et al. 2008) and it is one of the most common causes of aseptic meningitis in unimmunised populations. It is less commonly associated with encephalitis and para-infectious encephalopathy. The differential diagnosis of parotitis with CNS involvement includes EBV, influenza, para-influenza, HHV-6, coxsackievirus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, HIV, bacterial infection, drugs and tumours (Davidkin et al. 2005; Hvidt et al. 2008).

Diagnosis of mumps meningoencephalitis is most reliably achieved by CSF PCR. Viral culture or PCR of buccal or parotid gland duct swabs (following 30 seconds of parotid gland massage) may detect the virus within 9 days of symptom onset, and urine samples for a further 5 days (Kneen et al. 2012). Infection may also be diagnosed serologically by measurement of specific IgM (Hvidt et al. 2008). Elevated serum amylase is commonly seen in acute mumps infection (Solomon et al. 2007).

Mumps virus meningitis

Mild degrees of CSF pleocytosis are observed in up to half of all cases of mumps (Russell and Donald 1958), with clinical meningitis occurring in up to 10% (Rubin et al. 2015) and marked elevation of lymphocyte count in 0.5–2%. Onset of symptoms including headache, vomiting, neck stiffness and lethargy is typically 5 days after onset of parotitis, although parotitis may precede meningitis by up to 3 weeks, follow it by up to 1 week, or be completely absent (30–40% of cases) (Levitt et al. 1970). Symptoms peak at around 48 hours and resolve in 7–10 days (Hvidt et al. 2008). CSF lymphocyte count may be as high as several hundreds of cells per mm³. The glucose content may be reduced (Wilfert 1969). Mumps meningitis is a benign, self-limiting illness without mortality or long-term sequelae (Hvidt et al. 2008; Stahl et al. 2011), although obstructive hydrocephalus is reported as a rare complication (Yanofsky et al. 1981; Lahat et al. 1993). Pleocytosis may last for several months and there is protracted persistence of specific intrathecaully-produced oligoclonal IgG (Vandvik et al. 1978a).

Mumps encephalitis and para-infectious encephalopathy

Encephalitis occurs in up to 0.5% of mumps cases (Rubin et al. 2015) although severe disease is rare, occurring in one per 6000 cases or less (Cooper et al. 2007). Symptoms include seizures, alterations of consciousness and focal neurological signs (Koskineni et al. 1983). Predominant involvement of
the cerebellum is frequently observed (Cohen et al. 1992). Multifocal seizures are described (Parain and Boulloche 1988). Pathological findings include oedema and congestion throughout the brain with haemorrhage, lymphocytic perivascular infiltration and demyelination (Johnson 1982a; Rubin et al. 2015). Outcome is generally favourable in children and mortality is less than 1.5% (Hviid et al. 2008). Chronic infection may become established in some cases (Ito et al. 1991). Sequelae include sensorineural hearing loss (Hviid et al. 2008), ataxia and opsoclonus (Ichiba et al. 1988), vestibular neuritis (Thomke and Hopf 1992) and vertigo (Wilfert 1969).

Mumps virus is occasionally associated with rapid onset of progressive coma and/or seizures early in the febrile illness with normal CSF, suggesting a para-infectious encephalopathy. CSF cytokine profile is similar to that seen in influenza-associated encephalopathy (Watanabe et al. 2013). Specific syndromes described include acute infantile bilateral striatal necrosis (IBSN) (Goutieres and Aicardi 1982), acute necrotising encephalopathy (Watanabe et al. 2013) and clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) (Takanashi 2009) (see section Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses). The latter is also described following mumps vaccination (Takanashi et al. 2015).

**Henipaviruses**

Nipah virus and Hendra virus are two zoonotic paramyxoviruses that emerged as causes of encephalitis in the 1990s and were classified together in a relatively recently identified genus called *Henipavirus*. In both viruses, bats are the reservoir and mammals are amplifying hosts (horses for Hendra virus, pigs for Nipah virus). For humans the principal groups at risk are those working closely with the amplifying hosts. Hendra virus has so far occurred only in Australia. Nipah virus emerged in Malaysia but has now spread throughout Southeast Asia where outbreaks occur annually, particularly in India and Bangladesh (Wilson 2013). A recent outbreak demonstrated human-to-human transmission via respiratory droplets (Sazzad et al. 2013) and the virus can present with respiratory symptoms. Both viruses cause a devastating encephalitis characterised by CNS vasculitis and brainstem involvement, with mortality of 40–75% (Eaton et al. 2006). Acute neuroimaging may reveal multiple small T2-hyperintensities throughout the cerebral white matter (Kastrup et al. 2008). Survivors suffer motor deficits (Goh et al. 2000) and chronic intraneuronal infection is described as a cause of relapse. A recent review of emerging infections flagged Nipah virus as a special threat in view of its high mortality rate, wide host range and ability to spread from human to human (Wilson 2013). Other henipaviruses circulate widely in African fruit bat populations and the continent is considered high risk for future emergence of henipaviruses infecting humans.

**OTHER VIRUSES**

**Rabies Virus**

Rabies is caused by several species or genotypes of *Lyssavirus*, the most important of which in humans is genotype 1, also known as rabies virus. It is rare in industrialised countries but causes an estimated 50,000 deaths per year in Africa and Asia (Stahl et al. 2011). It is a non-arthropod-borne zoonotic virus transmitted to humans in the saliva of infected mammals (e.g. bats, dogs, foxes, cats, raccoons, etc.) via a bite or skin abrasion, and occasionally through intact skin or mucous membranes. A history of animal bite is absent in many cases (Fishbein and Robinson 1993). A small number of infections have been acquired via organ donation (Burton et al. 2005).

Viral replication in the skin is followed by retrograde axonal transport of virus along the peripheral nerve and eventually CNS invasion. The incubation period lasts between 10 days and 8 months. Severe bites to the face and neck are associated with shorter incubation time (Dimaano et al. 2011). A brief prodrome of fever and malaise precedes onset of neurological symptoms. In classic furious rabies (two-thirds of cases) the predominant feature is altered mental status (fluctuating delirium with intermittent agitation). Characteristic symptoms such as hydrophobia, aerophobia, hypersalivation, hyperacusis and pharyngeal spasms are striking but may be absent in some cases. Paralysis and respiratory failure may follow on from furious rabies, or may be the presenting neurological features in paralytic rabies (one-third of cases) (Hemachudha et al. 2013). Disease progression to coma and death is almost universal in symptomatic patients, although occasional cases of survival have been reported using modern intensive care support (Willoughby et al. 2005). Survival may be associated with the presence of neutralising antibodies in the CSF and non-*Lyssavirus* 1 disease (Wilde et al. 2008). In cases following organ donation, CSF analysis revealed mild pleocytosis, and MRI revealed T2-hyperintensity in the hippocampi, brainstem, temporal lobes and basal ganglia (Burton et al. 2005). Characteristic viral inclusions (Negri bodies) are found in the neurons, especially in the pyramidal cells of the hippocampus. PCR amplification and/or antigen detection can also be undertaken on brain biopsy, which should be considered in cases of encephalopathy where exposure may have occurred (Hughes et al. 2004).

When a suspected exposure has occurred, prevention of rabies may be achieved by rapid post-exposure prophylaxis, either passively with human rabies immunoglobulin, or actively with serial vaccination on days 0, 3, 7, 14 and 28 (Willoughby and Hammarin 2005). Pre-exposure prophylaxis is indicated in certain circumstances (occupational, travel).

**Human Immunodeficiency Virus**

Primary HIV-1 infection can present with an acute meningoencephalitis during seroconversion (Apoola et al. 2002), although it is unusual in children. HIV should be considered in
the differential diagnosis of aseptic meningitis if there are risk factors in the history. The effects of chronic HIV infection on the brain are discussed in the Chronic Viral Infections section.

Parvovirus B19

Parvovirus B19 is a ubiquitous DNA virus of the family Parvoviridae, 60% of adults have a history of previous exposure (Douvoyiannis et al. 2009). Most infections are asymptomatic but the virus is also well known as the cause of erythema infectiosum or ‘slapped cheek syndrome’ in children. In addition, parvovirus may account for up to 4–5% of undiagnosed meningoencephalitis in childhood (Barah et al. 2001). Around one-third of cases occur in the immunocompromised (Douvoyiannis et al. 2009; Barah et al. 2014). Susceptibility in immunocompetent children may be influenced by HLA genotype (Kerr et al. 2002) and host immune response may contribute to encephalopathy in some cases.

The most common CNS presentation is encephalitis (Barah et al. 2014). Classic erythema infectiosum rash is seen in only a third of cases, and even less in the immunocompromised. Neurological features are of a nonspecific encephalitis syndrome with or without cerebellar involvement. Onset of neurological symptoms may be before, during or after onset of rash. Parvovirus has a tropism for erythroid progenitor cells (Heegaard and Brown 2002) and 44% of children with encephalitis demonstrate anaemia (Barah et al. 2014); stroke secondary to aplastic crisis should be considered as a differential for neurological impairment in children with sickle cell disease (Douvoyiannis et al. 2009). CSF pleocytosis is observed in around half of encephalitis cases (Barah et al. 2014). Viral DNA is usually detected in the CSF and CSF anti-B19 IgM is detectable in one-third of cases (Douvoyiannis et al. 2009). Serum anti-B19 IgM may also support the diagnosis. MRI may be normal or demonstrate nonspecific white matter T2-hyperintensity and mild ventriculomegaly (Kerr et al. 2002; Douvoyiannis et al. 2009; Barah et al. 2014).

IVIg is often used in parvovirus infection to neutralise the virus, although the mechanism of action is not fully understood (Barah et al. 2014). Encephalitis cases are often treated with steroid and IVIg although evidence of efficacy is mixed (Douvoyiannis et al. 2009; Barah et al. 2014). Outcome is variable with up to 14% mortality and neurological sequelae including language impairment and developmental delay in up to 26% (Barah et al. 2014). Other reported CNS manifestations of parvovirus include aseptic meningitis (with good prognosis), transverse myelitis and Reye syndrome (Barah et al. 2014). Some cases of anti-NMDA receptor encephalitis may be triggered by parvovirus (Grillo and da Silva 2013).

Rubella Virus

Rubella virus is a single-stranded RNA virus of the family Togaviridae. Congenital rubella infection is a cause of severe neurological disease. Postnatally acquired infection, which is now rare in vaccinated settings, may be asymptomatic or cause an exanthematous febrile illness (German measles). Severe encephalitis is described in 1 per 5000 cases. The mechanism is unclear and may be due to direct invasion and/or be immune-mediated. It may occur simultaneously with the rash or up to a week later; rash may be absent in 15–19% of cases (Bahloul et al. 2013; Chaari et al. 2014). Clinical features include agitation, confusion and seizures. Severity is variable; comatose presentation requiring intensive care admission is described (Bahloul et al. 2013). Serum anti-rubella IgM is usually detected during the acute illness, and is also detected in the CSF in around half of cases (Bahloul et al. 2013). Detection of rubella in urine by culture or PCR may support the diagnosis (Kneen et al. 2012). Management is supportive only. Mortality in the modern era is 8–9.5% (Bahloul et al. 2013; Chaari et al. 2014) with full recovery reported in the majority of survivors.

Rotavirus

Rotavirus comprises five species of double-stranded RNA virus in the family Reoviridae. It is the most common cause of childhood gastroenteritis worldwide (Parashar et al. 2003). Rotavirus infection was previously thought to be restricted to the epithelial cells of the gut, but following findings of circulating rotavirus antigen and RNA in the majority of infected children (Blutt et al. 2003), it is now understood as the cause of a range of extra-intestinal complications (Blutt and Conner 2007). Neurological manifestations include meningoencephalitis, encephalopathy, cerebellitis and seizures. The mechanisms of CNS involvement are not fully understood. Some cases are likely due to direct viral invasion, as suggested by the presence of rotavirus RNA in the CSF, but others may be para-infectious phenomena induced by the rotavirus enterotoxin NSP4 (Dong et al. 1997; Estes and Morris 1999), leading to neuronal cell membrane destabilisation (Tian et al. 1996), elevated CSF nitric oxide levels (Kawashima et al. 2004) and/or neuroinflammation. Variability in NSP4 between strains may be the explanation for observed variations in pathogenicity (Goldwater et al. 2001). Management of rotavirus infection is supportive only. The incidence of gastroenteritis has reduced since routine vaccination for rotavirus was introduced to the United Kingdom in 2013 (Bawa et al. 2015); it is hoped that the burden of neurological disease will decrease accordingly in future.

Seizures

Prevalence of seizures in children hospitalised with rotavirus infection is 4–7% (Johansen et al. 2008; Le Saux et al. 2010; Lloyd et al. 2010). Seizures may be febrile or afebrile and typically start on the third day of illness (Bass et al. 2007). Most are brief and generalised (Lloyd et al. 2010). CSF analysis and neuroimaging are normal in the majority of cases (Lloyd et al. 2010) although PCR reveals the presence of rotavirus in the CSF in some (Liu et al. 2009). Electrolyte abnormalities and cerebral sinovenous thrombosis should also be considered as secondary causes of seizures in children.
with severe diarrhoeal illness. Outcome is excellent with only 7% of children requiring chronic anticonvulsant therapy in one series (Lloyd et al. 2010). Rotavirus vaccination is associated with an 18–21% reduction in seizure incidence over the following year (Payne et al. 2014).

Neonatal rotavirus infection has recently been described as a cause of seizure onset on days 4–6 of life with white matter injury on MRI (Lee et al. 2014; Yeom et al. 2015). Changes are best visualised on diffusion-weighted imaging, appearing as diffuse symmetrical lesions in the cerebral white matter and corpus callosum with restricted diffusion (Lee et al. 2014). In most cases rotavirus is detected in the stool but not the CSF (Yeom et al. 2015), suggesting a para-infectious mechanism of CSF involvement, possibly toxin mediated (de Vries and Bearden 2015). Cystic evolution of white matter changes is described in some cases with neurodevelopmental sequelae (Verboon-Maciolek et al. 2012).

**Encephalitis and Encephalopathy**

Encephalitis is a rare complication of rotavirus infection (Hongou et al. 1998; Kehle et al. 2003; Goto et al. 2007). One series of 984 children hospitalised with rotavirus gastroenteritis found a 1.7% prevalence of encephalitis with abnormal EEG (Johansen et al. 2008). Most cases occur in children aged 6–24 months. The typical history is of encephalopathy and seizures presenting on day 2–3 of gastroenteritis. CSF pleocytosis is observed in 48% and EEG is abnormal in 91% of cases. Three-quarters of children enjoy full recovery without sequelae (Dickey et al. 2009).

Encephalopathy without encephalitis is also described in association with CNS penetration (Nakagomi and Nakagomi 2005). Associated syndromes include haemorrhagic shock and encephalopathy syndrome (HSES) (Kuki et al. 2015), clinically mild encephalitis/encephalopathy with reversible splenial lesion (MERS) (Takanashi 2009), acute necrotising encephalopathy and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) (Hoshino et al. 2012) (see the Acute Encephalopathy Syndromes Occurring in Association with Viral Illnesses section).

**Cerebellitis**

There are several case reports of cerebellitis associated with rotavirus infection in children (Nigrovic et al. 2002; Shiihara et al. 2007; Dickey et al. 2009; Kobayashi et al. 2010; Kubota et al. 2011; Thompson et al. 2012). Symptoms include ataxia, agitation, behavioural arrest, dysphasia and mutism. Presence of rotavirus RNA in the CSF is variable. MRI typically reveals focal or diffuse cerebellar T2-hyperintensity with or without restricted diffusion. Acute neurological impairment may persist for weeks to months and chronic sequelae including dysarthria and cognitive difficulties are reported (Thompson et al. 2012).

**Lymphocytic Choriomeningitic Virus**

Lymphocchoriomeningitis virus (LCMV) is a zoonotic arenavirus which can rarely cause aseptic meningitis in humans. The reservoir host is the house mouse and the virus is found worldwide. Human infection is acquired following contact with excreta of infected mice, guinea pigs or hamsters, and can also be acquired vertically and via organ transplantation (Fischer et al. 2006). Postnatally acquired infection is usually either asymptomatic or associated with an influenza-like illness, but a CNS syndrome is also described (Barton and Hyndman 2000). Neurological features in the immunocompromised include meningoencephalitis (characterised by markedly elevated CSF protein in the presence of mild lymphocytic pleocytosis) (Fig. 11.20) and subdural effusions (Fischer et al. 2006).
The virus is difficult to detect by culture or PCR. Ribavirin has proven efficacy in the treatment of other arenaviruses and may be used empirically in suspected lymphohorioni meningitis virus infection in the immunocompromised (Wilson 2013).

**CHRONIC VIRAL INFECTIONS**

Viral infections of the CNS in children may present as subacute or chronic meningitis, encephalitis or myelitis syndromes. Immunocompromised children are especially susceptible to viral agents presenting in this manner, including measles (inclusion body encephalitis), enteroviruses, HIV, and several of the herpesviruses. Subacute onset of CNS viral infection is unusual in immunocompetent children in the era of measles vaccination, which has greatly reduced the incidence of subacute sclerosing panencephalitis (SSPE) (Campbell et al. 2007). Most of the chronic encephalitides are primary, with presence of the responsible organism in the CNS; they form a heterogeneous group that includes well-defined types (e.g. SSPE, rubella panencephalitis, HIV encephalopathy, human T lymphocytic virus myelitis) and poorly understood cases that are possibly not directly due to virus infection. The mechanisms of chronic viral encephalitis are complex and vary according to the interaction between the infecting agent and the host immune response. The well-defined types are reviewed below.

**MEASLES VIRUS**

Measles virus causes two distinct chronic encephalitides.

**Measles Inclusion Body Encephalitis**

Measles inclusion body encephalitis, also known as subacute measles encephalitis, is a rare, chronic encephalopathy occurring as a delayed complication of measles several months after primary infection. It is observed mainly in immunocompromised patients (Murphy and Yunis 1976), particularly those with acute lymphoblastic leukaemia (Hughes et al. 1993), although it occasionally occurs in apparently immunocompetent children. Contrary to the usual post-infectious encephalitis (i.e. ADEM), the measles virus is present in large quantities within the brain; paramyxovirus nucleocapsid inclusion bodies are visualised within cells by electron microscopy and measles RNA is detected by reverse transcriptase-PCR. Focal necrosis is the main histological finding (Mustafa et al. 1993). The inflammatory reaction is variable but often inconspicuous (Lacroix et al. 1995).

The disease presents 2–12 months after measles infection, case contact or vaccination, although a history of these is absent in up to 18% of cases (Mustafa et al. 1993). Average age is 6 years. Nearly all cases present with altered consciousness and seizures (Buchanan and Bonthius 2012). Epilepsia partialis continua is the first manifestation in many cases (Aicardi et al. 1977; Luna et al. 1990; Barthez-Carpentier et al. 1992). Focal seizures are often recurrent, treatment-refractory and associated with Todd paralysis (Buchanan and Bonthius 2012). Progressive deterioration leads to coma. Other neurological signs may include focal motor deficits, language impairment, visual impairment, and dysphagia (Mustafa et al. 1993). In some patients, a retinopathy is present (Haltia et al. 1977).

Diagnosis can be challenging as CSF may initially be normal or show only slight changes. In the majority of cases there is intrathecal synthesis of measles virus antibody with rising titres detectable in the CSF and high antibody titre in the serum also. In the most severely immunosuppressed children, however, antibody production may be impaired. MRI is usually normal at presentation, later demonstrating nonspecific abnormalities including oedema, atrophy and ventriculomegaly (Bitnun et al. 1999). The EEG may show background slowing with repetitive slow-wave complexes at a rate of about 1Hz (Aicardi et al. 1977, Colamaria et al. 1989).

The course is fatal in three-quarters of cases, with death usually occurring within weeks of onset (Buchanan and Bonthius 2012). Management is largely supportive. A few cases have been treated with intravenous ribavirin but survivors are left with severe sequelae (Mustafa et al. 1993).

**Subacute Sclerosing Panencephalitis**

Subacute sclerosing panencephalitis (SSPE) is a devastating long-term degenerative complication of continued abortive measles virus replication in the CNS subsequent to primary infection (Connolly et al. 1967). Diagnosis of SSPE is made after two per 100 000 measles infections but the actual rate is estimated to be four to 11 per 100 000 (Bellini et al. 2005, Campbell et al. 2007). A rate of one per 1 million is reported in vaccinated children, but these cases are caused by wild type not vaccine strains of measles (Jin et al. 2002; Miller et al. 2004); that is, vaccination does not cause SSPE (Bellini et al. 2005; Campbell et al. 2007). The interval between primary infection and symptom onset is up to 7 years. SSPE is more common in children who had primary measles under 2 years of age. Perinatally-acquired infection may result in a shorter latency and more fulminant course (Campbell et al. 2007).

**Clinical features of SSPE**

Early clinical diagnosis is challenging as the first stage of illness is characterised by subtle progressive symptoms (Honarmand et al. 2004). In two-thirds of cases there are personality changes and insidious intellectual deterioration with an aphasic-apraxic-agnostic predominance. Often, such children are regarded as suffering from psychological problems and referred to psychiatric clinics. In a quarter of patients neurological signs or seizures are the first manifestations. Involuntary movements usually appear within 2–3 months and are characteristic of the second stage. The movements may be myoclonic jerks; the differential diagnosis of dementia with myoclonic jerks includes Creutzfeldt–Jakob disease. Usually they are more complex, involving several successive limb segments in a repetitive
pattern. Onset of each movement is abrupt, but the duration is longer than that of a common myoclonic jerk, often lasting several seconds. Abnormal movements recur periodically, although the intervals between two jerks are not equal and may vary from day to day in the same patient. The movements are usually bilateral, but strictly unilateral jerks may occur. They are absent during sleep and may disappear and reappear without apparent reason. In some patients, they may be replaced or preceded by periodic manifestations more typical of epilepsy, in particular by a tonic with head nods or complete falls, or rarely by typical myoclonias. Generalised epileptic seizures, absence-like fits or partial seizures are uncommon (Andermann 1967; Kornberg et al. 1991). In the third stage, extrapyramidal or pyramidal dysfunction, or both, become prominent. Extrapyramidal dyskinesias may appear, and parkinsonian rigidity is common. Dementia is severe and the child is bedridden. The terminal stage is characterised by progressive unresponsiveness, worsening hypotonia or decerebrate rigidity, swallowing and respiratory difficulties, and autonomic dysfunction. The median duration of the disease is about 12 months and the course is usually regularly progressive. Subacute forms, lethal in as little as 6 weeks, are occasionally seen (Nihei et al. 1977). Contrariwise, long periods of arrested progression may occur. Periods of spontaneous remission may last up to several years (Risk and Haddad 1979).

Ocular manifestations occur in over half of cases (Babu and Biswas 2007) and consist mainly of bilateral choroidoretinitis, which preferentially involves the macular area and may be associated with pallor of the disc. This may appear months or even years before the classic manifestations of SSPE (Robb and Watters 1970). Optic neuritis with atrophy is also described, and less commonly cortical blindness. Papilloedema can be observed with transient increases of ICP. The electroretinogram is normal but visual evoked potentials are impaired. Cases with lateralising or other focal features may pose a diagnostic challenge. Spastic hemiplegia and unilateral spasms may occur. Some cases present with cortical blindness or hemianopia and may be confusing. Occasionally, signs of intracranial hypertension in association with focal features may wrongly suggest a tumour (Glowacki and Goscinski 1973).

Diagnosis of SSPE

The spectrum of EEG abnormalities in SSPE is wide. The hallmark finding of periodic complexes is observed in 80% of cases. Characteristic abnormalities may be observed before any clinical manifestation (Wulff 1982) but they are most often detected during the stage of motor dysfunction (Praveen-Kumar et al. 2007). The complexes typically are formed of high-voltage polyphasic slow-wave complexes recurring periodically in association with clinical jerks although they may also occur in the absence of clinical manifestations. Their duration ranges from 0.5 to 2 seconds and they recur at 4–15-second intervals. They are usually identical in shape in any given lead. In some cases bursts of spike–wave activity may replace the typical complexes. Background tracings may be initially normal but become progressively slower while the amplitude diminishes.

Diagnosis of SSPE is confirmed by evidence of high titre measles antibody (IgG) in CSF and serum, with a very high CSF:serum antibody titre ratio. The CSF contains no cells, and the total protein is normal or slightly elevated. The virus cannot usually be amplified from the CSF, although viral genome may be amplified from brain tissue. In the early stages MRI may be normal, or demonstrate reduced grey matter volume in the fronto-temporal cortex, amygdala and cingulate gyrus (Aydin et al. 2009). Later neuroimaging reveals T2-hyperintensity in the cortex, basal ganglia and brainstem and asymmetrical changes in the periventricular white matter. The final stage is one of diffuse cortical atrophy (Buchanan and Bonthius 2012); however, the correlation between MRI appearance and clinical progression is poor (Ozturk et al. 2002).

Management of SSPE

Management of SSPE remains largely symptomatic; evidence of efficacy for antiviral agents in various combinations is mixed. Isoprinosine seems to induce remission in some cases (DuRant et al. 1982). A combination of intraventricular interferon and isoprinosine was reported to increase the rate of remissions from 5–10% to 45% (Yalaz et al. 1992; Gascon et al. 1993), but late recurrences may occur after several years of remission (Aylar et al. 1997). In a small randomised controlled trial, oral isoprinosine alone was compared with oral isoprinosine and intraventricular interferon-alpha2b. No group difference was detected but overall rates of satisfactory outcome (stabilisation or improvement) of around 35% were higher than historical spontaneous remission rates of 5–10%, suggesting that treatment is superior to no treatment (Gascon 2003). Other combination treatments used have included ribavirin (both intraventricular and intravenous) with isoprinosine (Aydin et al. 2003; Hosoya et al. 2004). Death occurs within 2–4 years of disease onset in most cases (Cobb et al. 1984).

Human Immunodeficiency Virus

HIV-1 is a retrovirus that infects cells that carry the CD4 receptor and a chemokine co-receptor (e.g. CCR5, CXCR4), including helper T lymphocytes (CD4 cells) and monocytes. Infants may be infected with HIV in utero, at birth, or during breastfeeding, but the majority are infected around the time of delivery. Maternal plasma HIV viral load is the most important predictor of infant infection with HIV, but perinatal delivery, prolonged rupture of membranes, presence of other sexually transmitted infections, chorioamnionitis and interventional vaginal delivery all increase the risk of transmission (Abrams et al. 1995; Peckham and Gibb 1995).

In non-breastfeeding populations, 15–20% of infants are infected compared to 30–40% in breastfeeding populations (ECS 1991, 1994; Newell et al. 2004). Interventions including antiretroviral therapy (ART) in pregnancy, during delivery and post-partum, prelabour caesarean section and avoidance of breastfeeding can reduce mother to child transmission of HIV to around 0.5% (Townsend et al. 2014). In younger
children, due to persistence of transplacental maternal antibodies, direct methods of identification must be used to diagnose HIV infection including HIV RNA PCR, HIV DNA PCR, or proviral HIV DNA amplification. In older children suspected of having perinatally-acquired HIV, HIV serology can be used to screen for infection but PCR must be used to confirm the diagnosis and assess need for ART. Advancement of HIV disease and requirement for antiretroviral treatment is defined by clinical assessment and measurement of the CD4 count and plasma HIV viral load (Bamford et al. 2015).

Neurological complications of perinatally-acquired HIV infection may be caused by direct effects of HIV itself or secondary to opportunistic infections, other co-infections, cerebrovascular disease, autoimmunity, malignancy or toxicity of antiretroviral medication.

HIV is a neurotropic virus, although productive infection in the CNS is probably limited to macrophages and microglia. Brain involvement occurs very soon after infection, and infected microglia have been identified as early as 7 days after transfusion of infected blood. In vitro, HIV-induced expression of ICAM-1 on human brain microvascular endothelial cells increases the margination of inflammatory cells in the brain vasculature, leading to increased targets for HIV infection within the CNS (Stins et al. 2003). A small paediatric study demonstrated a relationship between T cell inflammatory mediators in CSF and CSF HIV viral load (McCoig et al. 2004). HIV in the CNS promotes an inflammatory process, which leads over time to cell death and neuronal loss, probably by the process of apoptosis (Epstein and Gendelman 1993). Pathological findings (Sharer et al. 1986) include diminished brain weight for age. Inflammatory cell infiltrates consisting of microglia, lymphocytes, plasma cells and, especially, multinucleated giant cells are distributed throughout the brain but are more prominent in the deep structures, including the basal ganglia and brainstem. Prominent inflammatory changes and calcification of small or medium-sized vessels are present, especially in the deep brain structures. These may explain the occurrence of ischaemic infarcts and strokes in children with HIV (Frank et al. 1989; Park et al. 1990). The spinal cord only rarely shows the vacuolar myelopathy which is frequent in adults (Dickson et al. 1989). Studies in HIV-infected adults have shown a reduction in CNS immune activation with combination ART, but low level immune activation persists on fully suppressive ART with likely deleterious neurological effects (reviewed in Winston and Vera 2014).

The original Centers for Disease Control and Prevention (CDC) classification of HIV disease in children included a number of different presentations of ‘HIV encephalopathy’: failure to attain or loss of developmental milestones and intellectual ability; impaired brain growth or an acquired microcephaly; and acquired symmetrical motor deficit (CDC 1994). These different clinical presentations have differing aetiologies relating not just to activity of HIV in the CNS but also to progression of immune deficiency and opportunistic infections manifesting in the CNS (Mitchell 2001).

Around 20% of HIV-infected children become severely symptomatic or die in the first year of life. These ‘rapid progressor’ infants are more likely to be born to mothers with more advanced HIV disease, and they are at highest risk of early presentation with HIV encephalopathy (Blanche et al. 1994; Lobato et al. 1995; Tardieu et al. 2000). Overall, up to 10% of HIV-infected children have signs of encephalopathy, usually presenting with motor impairment and developmental delay. More subtle cognitive abnormalities occur in at least 30% of children with HIV, and many have speech and language difficulties and problems with school performance (Tardieu et al. 1995; Pearson et al. 2000). Infants classically present with developmental delay, microcephaly and a diplegic motor impairment. This is often in association with other opportunistic infections including cytomegalovirus and *Pneumocystis jirovecii* pneumonia. In one detailed study from the United States, infants infected with both HIV and CMV had a significantly increased risk of CNS disease and a worse long-term neurological prognosis (Kovacs et al. 1999). These infants present like other children with cerebral palsy with a fixed neurological insult and consequent developmental problems; they do not demonstrate a pattern of progressive dementia as seen in adults or older children infected with HIV when the brain is more mature (Tardieu et al. 2000).

CT in symptomatic children has demonstrated brain atrophy in over three-quarters of cases, with increased white matter attenuation and calcification of the basal ganglia in approximately a quarter (Belman et al. 1986; DeCarli et al. 1993; Pearson et al. 2000) (Fig. 11.21). MRI shows high signal from the white matter and cortical atrophy in most cases (Chamberlain et al. 1991; Pavlakis et al. 1995). A more recent MRI study from Africa has shown white matter signal abnormalities to be present from very early on in perinatal HIV infection, even in the context of early ART initiation (Ackermann et al. 2014). The relevance of these white matter changes to neurodevelopmental outcome remains to be explored. In a small study of 39 children (aged from <1 year to 13 years), the level of HIV viral load in the CSF was related to severity of cortical atrophy, but not to intracerebral calcification (Brouwers et al. 2000). In addition, basal ganglia calcification was not related to the severity of the neurological symptoms. In HIV encephalopathy the CSF is most often normal but may contain a mild excess of lymphocytes associated with a modest, often transient, elevation of protein.

In the era before successful treatment of HIV, only around 50% of affected children survived to 10 years of age, and those with neurological signs or symptoms had a very high risk for rapid disease progression at all ages (Pearson et al. 2000). Thirty to fifty per cent of children in the pre-combination ART era developed HIV encephalopathy (Epstein et al. 1988). With the advent of combination ART, the majority of HIV-infected children are likely to survive long-term (Gibb et al. 2003). In addition, there has been a dramatic decrease in the incidence of HIV encephalopathy (Patel et al. 2009). Adolescents in current cohorts with a history of severe immunosuppression/AIDS have been shown to have a higher risk
of neurocognitive and psychiatric impairment (Wood et al. 2009). Early identification of HIV-infected infants who may be at risk of encephalopathy is crucial, so that treatment may be started early enough to prevent permanent neuronal damage, if that is possible (Sanchez-Ramon et al. 2003). Within a French observational cohort, 40 infants who received ART before 6 months of age did not have early-onset severe HIV disease including encephalopathy during the first 24 months of life, whereas in the deferred therapy group (n=43), three developed encephalopathy (Faye et al. 2004). Although these numbers are small, treatment in infancy seems reasonable to attempt to prevent permanent neurological complications. However, where motor neuronal damage has already occurred in infancy, it is not surprising that it cannot be reversed by combination ART (Foster et al. 2006). However, it has been suggested that ART may prevent or improve more subtle neuropsychological/neurocognitive problems (Sanchez-Ramon et al. 2003). Early ART initiation was found to be associated with better neurodevelopmental outcomes in HIV-infected infants in a large prospective study in Africa (Laughton et al. 2012). Early HIV viral suppression has now also been shown to be associated with improved neurocognitive outcomes in a large US cohort study (Crowell et al. 2015). A smaller observational cohort study in the Netherlands found subtle neurocognitive impairment in a group of mainly ART-treated children, higher CD4 percentage at time of ART initiation and longer duration of ART being associated with better working memory and attention control respectively (Koekkoek et al. 2008).

A scoring system has been developed for potential CSF penetration of different ART drugs (Letendre et al. 2008). How this relates to concentrations in neuronal tissue and differing neurological outcomes in HIV-infected children is yet to be fully determined (Crowell et al. 2015).

Whether or not ART-treated survivors of vertical HIV infection will have an increased risk of early onset of HIV dementia or other neurological syndromes in adult life can only be speculated at this stage. The importance of monitoring for potential acute and long-term neurotoxicity of antiretroviral drugs continues to be an essential aspect of clinical care of HIV-infected children and adolescents as they transition to adult services. A recent cohort study of 59 children with perinatally-acquired HIV found 22% to have language impairment, 14% abnormal muscle tone and 12% delay in reaching developmental milestones. Ventricular enlargement and sulcal widening (29%) and white matter lesions (38%) were common (van Arnhem et al. 2013). Although this cohort included a significant number of children from the pre-combination ART era, it is likely to be representative of the current clinical cohort in Europe and the United States and increasingly in the African setting and we should focus efforts on optimising care for these children and adolescents as they progress to adult life while optimising treatment strategies to minimise the risk of neurological disease in children born with HIV today.

**HUMAN T LYMPHOCYTE VIRUS**

Human T lymphocyte virus type 1 (HTLV-1) was the first human retrovirus to be identified. It is associated with adult T cell malignancies and is the causal agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in children and adults. Approximately 15–20 million people are infected worldwide, mostly in West Africa, South America, the Caribbean and Japan (Verdonck et al. 2007). It is uncommon in Europe but has been reported in at-risk groups including immigrants from endemic areas, sex workers
and injecting drug users (Zehender et al. 2004). Transmission occurs via contact with infected bodily fluids including blood and breast milk. Mothers who breastfeed for longer, have higher breast milk viral load and have greatest HLA concordance with their children are more likely to transmit the infection (Wiktor et al. 1997; Li et al. 2004; Biggar et al. 2006). Infection is mainly of CD4+ T cells (Satou and Matsuoka 2010); 0.25–4% of carriers develop HAM/TSP, by incompletely understood mechanisms (Verdonck et al. 2007). There is a female predominance. There is a latency period of many years; onset is usually in the fourth or fifth decade of life. Cases in children are documented as young as 6–7 years (Roman 1988; Gessain and Gout 1992). Pathologically, HAM/TSP is characterised by infiltration of the white and grey matter of the spinal cord with CD4+ T cells and macrophages. HTLV-1 RNA is detectable within lesions (Lehky et al. 1995). HTLV-1 is also associated with a severe infective dermatitis in vertically infected children, which may occur along with early onset of HAM/TSP (Primo et al. 2005). Both conditions are probably related to the host anti-HTLV-1 immune response as well as HTLV-1 viral load (de Oliveira Mde et al. 2004; Sabourui et al. 2005). A rare smouldering retinal vasculitis with ultimate retinal degeneration has been reported in Japanese adolescents with HTLV-1 (Nakao and Ohba 2003). Short stature and anaemia may also be associated with HTLV-1 infection in children (Primo et al. 2005).

The clinical presentation of HAM/TSP has been better characterised in adults than children. It is a progressive chronic myelopathy with preferential damage to the lower thoracic cord (Aye et al. 2000), leading to symmetrical weakness, spasticity and hyperreflexia in the lower limbs with bladder and bowel dysfunction (Lairmore et al. 2012). Sensory involvement is mild (Primo et al. 2005). Intention tremor, optic atrophy and cerebellar signs are found in some patients and may occasionally be prominent (Kira et al. 1993). CSF may show mild lymphocytic pleocytosis with elevated protein. CSF/serum HTLV-1 antibody ratio is elevated (Verdonck et al. 2007). HTLV-1-specific T cells have been isolated in some cases (Kubota et al. 2002) and HTLV-1 proviral load may be elevated (Lezin et al. 2005). MRI in adults reveals multiple disseminated white matter lesions in the brain and spinal cord with perivascular demyelination (Lairmore et al. 2012); however, most paediatric cases have normal neuroimaging (Primo et al. 2005). Other causes of myelopathy must be excluded including spinal cord compression and parasites; HAM/TSP may present as a multiple sclerosis mimic with positive oligoclonal bands.

Oral or intravenous steroids are the mainstay of treatment, especially in early disease (Verdonck et al. 2007; Araujo et al. 2008; Pillat et al. 2011). Interferon-alpha may also be of some benefit (Izumo et al. 1996; Oh et al. 2005; Pillat et al. 2011). A small trial of zidovudine plus lamivudine did not find any benefit (Taylor et al. 2006). Sodium valproate, methotrexate, pentoxifylline, azathioprine and danazol have also been tried (Araujo et al. 2008). The typical course in children is of rapid progression over 2 years with considerable motor impairment and autonomic dysfunction. The family of affected children should be screened for HTLV-1 as familial clustering of HAM/TSP has been reported (Primo et al. 2005).

JOHN CUNNINGHAM VIRUS

John Cunningham virus (JCV) derives its name from the initials of the patient with progressive multifocal leuкоencephalopathy (PML) in whom it was first identified (Padgett et al. 1971). It is a ubiquitous, neurotropic human polyomavirus of the family Papovaviridae. It is the cause of progressive multifocal PML, a fatal demyelinating disease, in immunocompromised patients. It is now known to be a ubiquitous childhood infection, with over one-third of healthy individuals having seroconverted by adulthood (Kean et al. 2009). After asymptomatic primary infection (acquired by faeco-oral, respiratory, seminal or blood-borne transmission), JCV lies latent in the kidney, bone marrow, brain and lymphoid tissues (Stahl et al. 2011); it is detectable in the tonsillar tissue of 39% of healthy children (Monaco et al. 1998). PML develops due to reactivation of JCV in children with HIV (Berger et al. 2001) or other causes of immunocompromise including congenital immunodeficiency and treatment for haematological malignancy (Redfearn et al. 1993; Angelini et al. 2001; Demir et al. 2005). PML is also reported at initiation of antiretroviral treatment for HIV due to immune reconstitution inflammatory syndrome (PML-IRIS) (Nuttall et al. 2004). Over 400 cases of PML have been reported to date in patients receiving treatment with the therapeutic monoclonal antibody natalizumab for relapsing-remitting multiple sclerosis, but very few of these were in children, the youngest being 15 years old (Dong-Si et al. 2015). Risk of PML with natalizumab therapy can be stratified by duration of treatment, exposure to previous immunomodulatory drugs and JCV antibody status (Gorelik et al. 2010). Histopathological features of PML are of focal demyelination with abundant lipid-laden macrophages, bizarre astrocytes, and enlarged oligodendrocytes with intranuclear inclusions (Schwenk et al. 2014).

Clinical presentation of PML is variable and may be insidious with cognitive deterioration, or more rapidly progressive with seizures, hemiparesis, ataxia and dysarthria (Schwenk et al. 2014). Appearance on MRI is of asymmetrical, T2-hyperintense lesions mostly affecting the frontal and parieto-occipital subcortical white matter, without oedema or mass effect (Nickerson et al. 2012; Schwenk et al. 2014). The periventricular white matter is relatively spared (Fig. 11.22). Contrast enhancement is absent in 84% of cases (Schwenk et al. 2014). The spinal cord may also be involved (Bernal-Cano et al. 2007). CSF cell count, protein and glucose are usually normal. Definitive diagnosis can be achieved by detection of JCV DNA in the CSF, although sensitivity is only 59% (Schwenk et al. 2014).

Management focuses on restoration of immune function by reduction of immunosuppression (Pinto and Dobson
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2014; Schwenk et al. 2014). There are case reports of cidofovir being tried as antiviral therapy in both HIV-infected (Hugonenq et al. 2002; Robinson et al. 2004) and HIV-uninfected children (Angelini et al. 2001; Weber et al. 2011), with mixed results. Cytarabine (Aksamit 2001) and mirtazapine (Verma et al. 2007) have been tried in adults but also lack clear evidence of efficacy. PML-IRIS may be treated with steroids (Tan et al. 2009; Schwenk et al. 2014). Mortality is 69% in HIV-infected and 80% in HIV-uninfected children (Schwenk et al. 2014).

BK virus is a related polyomavirus which has been associated with meningoencephalitis in patients with HIV (Vallbracht et al. 1993; Bratt et al. 1999). There is increasing interest in the role of the polyomaviruses in neuro-oncogenesis (Crawford 2010), with JCV DNA detected in a significant proportion of paediatric medulloblastomas (Krynska et al. 1999) and ependymomas (Okamoto et al. 2005). However, a causal relationship has not yet been established.

### ENTEROVIRUSES

Chronic enteroviral meningoencephalitis is described in children with inherited or acquired antibody deficiencies such as Bruton disease (X-linked hypogammaglobulinaemia), HIV and common variable immunodeficiency (Cooper et al. 1983; Tormey et al. 2003). The clinical picture is of chronic lymphocytic meningitis with variable features of brain involvement such as insidious intellectual deterioration, disturbances of consciousness and focal seizures or neurological deficits. Other presentations include progressive myelopathy, myelopathy progressing to encephalopathy, pure encephalopathy, retinopathy, sensorineural hearing loss, and dermatomyositis (Rudge et al. 1996). The course is chronic and often fatal. Diagnosis is by PCR or culture of the CSF or biopsy tissue (Sawyer 2001). Quantitative PCR (see Box 11.1) may be used to monitor treatment efficacy (Quartier et al. 2000). Treatment by intrathecal and intraventricular injection of gammaglobulins may help to improve symptoms, but does not always clear infection (Erlendsson et al. 1985; Johnson et al. 1985; McKinney et al. 1987; Quartier et al. 2000). Pleconaril inhibits viral replication in some enteroviruses and has been efficacious in some cases (Tormey et al. 2003; Wildenbeest et al. 2012). However, the outcome of chronic enteroviral meningoencephalitis is usually fatal (Tormey et al. 2003). Enteroviruses may also be capable of persisting within the CNS in immunocompetent individuals but the long-term consequences are largely unknown (Rhoades et al. 2011).

### PROGRESSIVE RUBELLA PANENCEPHALITIS

A few children with congenital rubella (Townsend et al. 1975) and an occasional patient with acquired rubella (Lebon and Lyon 1974) have developed this very rare fatal panencephalitis (Stahl et al. 2011) with prominent cerebellar involvement some 10 years after primary infection. Insidiously progressive dementia is the first manifestation, followed by ataxia and myoclonic seizures. CSF examination shows mononuclear pleocytosis and increased protein with massive elevation of specific IgG (Vandvik et al. 1978b). Rubella virus has been isolated from the brain and leukocytes. Pathologically, inflammatory infiltrates and astrocytosis are prominent (Townsend et al. 1982; Frey 1997). The course is fatal in several years. No treatment is known.

### ENCEPHALOPATHIES OF OBSCURE ORIGIN THAT MAY BE RELATED TO VIRAL INFECTIONS

### BEHÇET SYNDROME

Behçet syndrome is rare in children but has been reported in infants as young as 2 months (Ammann et al. 1985). A transient form has been observed in infants born to affected mothers (Lewis and Priestley 1986). The disease features recurrent ulcerations of the mouth and genitalia, skin lesions often resembling erythema nodosum, anterior uveitis, keratitis, hypopyon and, less commonly, retinal involvement that in some cases may be isolated. CNS involvement is present in up to 25% of patients and may rarely precede the oculocutaneous
manifestations. Neurological manifestations include involvement of the cerebral hemispheres, spinal cord, cerebellum or brainstem (Nakamura et al. 1994). Pseudotumour cerebri with or without sinus thrombosis may be observed (Shakir et al. 1990). MRI may show disseminated areas of intense signal in T2 sequences (Wechsler et al. 1992; Saltik et al. 2004). The brainstem is consistently involved. Perivascular infiltrates with or without thrombosis are frequent (Wechsler et al. 1992). The disease may present as a cerebrovascular disease (Iragui et al. 1991) or as a chronic brainstem encephalitis (Ito et al. 1991). The diagnosis may be helped by the cutaneous sensitivity to mechanical trauma (pathergy). Behçet syndrome has a complex genetic aetiology; it is most common in those of Mediterranean and Eastern origin, although it also affects Caucasians. An enhanced inflammatory response and overexpression of pro-inflammatory cytokines are the prominent features of Behçet syndrome. This likely antigen-driven immune response in Behçet syndrome is possibly triggered by an infectious agent in a genetically susceptible host. Supporting this is the consistent association of disease susceptibility with polymorphisms in the human leukocyte antigen complex, particularly HLA-B*51. The diagnosis is a clinical one and so far there is no single laboratory test specific for the diagnosis of Behçet syndrome (Uziel et al. 1998; Marshall 2004). The immune modulating agents cyclosporin and azathioprine have performed well in clinical trials, and evidence is accumulating for the efficacy of anti-tumour necrosis factor therapy for certain types of Behçet syndrome.

RASMUSSEN ENCEPHALITIS

Rasmussen encephalitis is a chronic epileptic disorder (see also Chapter 16) characterised clinically by progressive neurological deterioration, focal seizures often progressing to intractable epilepsy, cognitive decline and hemispheric atrophy (Deb et al. 2005) (Fig. 11.15). The aetiology of this encephalitis remains unknown, and an autoimmune response triggered by a viral infection is a possibility. The multifocal distribution of pathological changes, as well as the heterogeneity in the stages of cortical damage in each patient, are consistent with an ongoing and progressive immune-mediated process of neuronal damage that involves neuroglial and lymphocytic responses, resembling other autoimmune CNS disorders such as multiple sclerosis (Pardo et al. 2004). A formal set of diagnostic criteria and a therapeutic pathway for the management have been proposed (Bien et al. 2005).

PRION DISEASES OF THE NERVOUS SYSTEM

Prions are infectious pathogens comprising abnormal forms of a protein encoded in the host genome (Collinge 2005). Prion disease is associated with accumulation of disease-related isoforms of the normal cellular prion protein (PrP	extsuperscript{c}). Different strains of prion occur despite the absence of any agent-specific genetic material. Folding of the proteins themselves may encode strain diversity with different subsequent effects on the host. Prion diseases include Creutzfeldt–Jakob disease (CJD), Kuru, Gerstmann–Sträussler–Scheinker disease (Brown et al. 1994) and fatal familial insomnia (Medori et al. 1992) in humans, and scrapie and bovine spongiform encephalopathy (BSE) in sheep and cattle. They are neurodegenerative conditions which can be classified as sporadic (85–90%), hereditary (10–15%) or acquired (1–3%) (Takada and Geschwind 2013). The pathogenesis of sporadic prion disease is not fully understood; hereditary cases are associated with mutations of the PRNP (Prion Protein) gene; and acquired forms are caused by transmission of infection from human to human or, as a zoonosis, from cattle to human (Prusiner and Hsiao 1994; Will 2003). The sporadic and hereditary types usually present in later life although sporadic CJD (sCJD) has been rarely reported in young people (Kulczycki et al. 1991). The pathological findings in CJD are of PrP	extsuperscript{Sc} deposition in the brain with fibrillary plaques and spongiform vacuoles, particularly in the cerebellum (Budka 2003). This section focuses on prion diseases as infectious diseases, that is, acquired prion diseases.

ACQUIRED CREUTZFELDT–JAKOB DISEASE

Most cases of iatrogenic Creutzfeldt–Jakob disease (iCJD) were acquired from human growth hormone treatment and dura mater grafts derived from cadaveric brain tissue with undiagnosed CJD infection (Billette de Villemeur et al. 1996; Billette de Villemeur 2003). Other sources included corneal grafts, gonadotrophic hormone, and improperly sterilised EEG depth electrodes and other neurosurgical equipment. Improved recognition of potentially infected individuals combined with modern sterilisation practices are thought to have largely ended the era of iCJD (Brown et al. 2012).

A novel human prion disease termed variant Creutzfeldt–Jakob disease (vCJD) emerged in the United Kingdom in the 1990s after changes in animal feeding and abattoir procedures led to human infection with the prion strain causing BSE in cattle (Will et al. 1996; Epstein and Brown 1997). Over 200 cases have been reported to date (Takada and Geschwind 2013), almost all in susceptible individuals with PRNP codon 129 polymorphism (Kaski et al. 2009). The number of cases still incubating in the UK remains unknown; analysis of 32,441 archived appendix samples found one in 2000 contained abnormal PrP (Gill et al. 2013). Four probable cases of vCJD occurred following transfusion of red blood cells from asymptomatic donors who subsequently developed the disease (Ironside 2012). However, incidence of vCJD has been declining since 1999–2000 (Ironside 2012) and national
surveillance of progressive intellectual and neurological deterioration in children since 1997 had, by 2009, identified only six children with vCJD (Verity et al. 2010).

Cases of CJD are reported in patients as young as 12 years (Heath et al. 2010). The presentation is with slowly progressive neurological disturbance manifesting mainly as dementia, myoclonus and cerebellar signs. Neuropsychiatric symptoms such as depression or mood swings may predominate for 6 months or more prior to onset of neurological symptoms (Takada and Geschwind 2013). Dysaesthesia is also reported (Corato et al. 2006). The hallmark MRI finding is the pulvinar sign, in which the posterior thalamus is brighter than the anterior putamen on T2- or diffusion-weighted imaging (Collie et al. 2003). Definitive diagnosis is based on identification of abnormal PrP in the brain via biopsy or autopsy. In vCJD, which unlike iCJD is acquired peripherally, the abnormal protein may also be identified in the lymphoreticular system by tonsillar biopsy (Will 2004). Assays to detect abnormal PrP in the blood and CSF may become available in future (Atarashi et al. 2011; Edgeworth et al. 2011).

Management of prion disease remains symptomatic only (Takada and Geschwind 2013). vCJD is universally fatal with a mean illness duration of 14 months (Corato et al. 2006). iCJD runs a faster course, leading to death within months of symptom onset in some cases (Brown et al. 1994; Deslys et al. 1994).

**MYCOTIC INFECTIONS OF THE NERVOUS SYSTEM**

Mycotic infections of the nervous system produce granulomatous meningitis or abscesses. In the majority of cases, mycotic infections occur as opportunistic infections in patients with immunodeficiency, indwelling devices or structural defects. As these infections are rare, advice regarding the most appropriate and up-to-date treatment should always be sought from microbiological specialists in the field. Outcomes from CNS fungal infection are often poor, but they are better than those reported in adult case series (Schwartz et al. 2011).

**ASPERGILLUS INFECTION**

Invasive aspergillosis is an uncommon but often lethal complication in severely immunocompromised patients. Conditions associated with CNS infection in infants and children include preterm birth haematological malignancy, solid organ and bone marrow transplant (especially in the context of prolonged neutropenia), advanced HIV disease and chronic granulomatous disease. Infection may cause brain abscesses, vasculitis, meningoencephalitis or encephalitis. Haemorrhage may occur most commonly into sites of infarction. *A. fumigatus* is the most common pathogen in the genus Aspergillus causing CNS infection. CNS Aspergillus infection may be associated with sinus or lung infection (Dotis et al. 2007). The eye and orbital structures may also become involved, leading to proptosis or ophthalmoplegia. Infection reaches the brain directly from the nasal sinuses or is blood-borne from the lungs and gastrointestinal tract. Single or multiple abscess formation with blood vessel invasion leading to thrombosis is a characteristic feature on neuropathological examination (Kleinschmidt-DeMasters 2002). Aspergillus should always be considered in immunocompromised patients with an acute onset of focal neurological deficits. Diagnosis of an intracranial mass lesion should be confirmed with neuroimaging (Fig. 11.23). Dual infections with other fungi may also occur, especially where the sinuses are the source. Direct examination and culture of tissue specimens is required to confirm the diagnosis, but treatment should be started on suspicion. Diagnosis may be supported by detection of fungal antigens using blood tests such as β-D-glucan or galactomannan (Leeflang et al. 2008; Wright et al. 2011). Though there are concerns regarding sensitivity and specificity of these assays, they may be used to monitor for early signs of fungal infection in at-risk individuals, to guide pre-emptive treatment and to monitor response to therapy (Wright et al. 2011). Fungal PCR are more recently being employed to aid diagnosis (Reinwald et al. 2013).

A combined approach with antifungal treatment and neurosurgical intervention with stereotactic removal of Aspergillus abscesses, granulomas and focally infected brain has demonstrated improved survival (Middelhof et al. 2005; Giacchino et al. 2006). Where possible, immunosuppressive treatment should be reversed and immune modulation to improve phagocytic function should be considered. The antifungal, voriconazole, which has excellent CNS penetration, has the most promising treatment results and is a recommended first-line therapy, liposomal amphotericin B being an alternative (Schwartz et al. 2005; Theuretzbacher et al. 2006; Schwartz et al. 2011; Blyth et al. 2014). Evidence for the use of combination or sequential antifungals in CNS aspergillosis is very limited but this strategy has been successfully employed in some case reports (Ehrmann et al. 2005; Schwartz et al. 2011; Hatipoglu and Hatipoglu 2013; Reminiac et al. 2014).

**CANDIDA INFECTIONS**

Candida species may invade the meninges from the bloodstream in cases of disseminated candidiasis. Such cases occur most commonly in relatively immune-incompetent preterm infants with prolonged hospital stay and frequent antibiotic exposure (Tripathi et al. 2012). Infants with congenital anomalies, with central venous access, receiving total parenteral nutrition, or with shunted hydrocephalus are most at risk of candidal
invasion of the CNS (Devlin 2006). Most neonatal fungal infections are due to *C. albicans*. The sources of candidiasis in neonatal intensive care units are often endogenous following superficial colonisation. Disseminated candidiasis presents like bacterial sepsis and can involve multiple organs such as the kidneys, brain, eye, liver, spleen, bone, joints, meninges and heart.

Candidal invasion of the CNS may also occur in children receiving myelosuppressive chemotherapy, most often for haematological malignancies. A more protracted period of neutropenia and receiving total parenteral nutrition increases the risk for CNS candida in these patients (McCullers et al. 2000). Confirming the diagnosis is difficult and requires culture of the organism from blood or other sterile bodily fluids (sensitivity of blood cultures is low): a high index of suspicion is required. Other candidal species, such as *C. tropicalis*, may also invade the CNS, and culture is important to ascertain sensitivity to antifungal treatment. In infants and children with risk factors, even a single colony of yeast in the CSF should not be considered a contaminant and treatment should be commenced before positive identification. Isolation of candida from a neonatal blood culture should prompt lumbar puncture (Faix 1984; Tripathi et al. 2012). As with Aspergillus infection (see Aspergillus Infection section), diagnosis of invasive candidal infection may be supported by detection of fungal antigen in blood through ELISA (Wright et al. 2011) or in CSF using PCR. First-line antifungal treatment options include liposomal amphotericin, fluconazole and echinocandins (e.g. micafungin). Some less common candida species are resistant to first-line agents. Isolation and identification of the organism can therefore guide empiric choice of first-line therapy prior to formal sensitivity results being available (Juster-Reicher et al. 2003; Tripathi et al. 2012). As is the case with CNS Aspergillus infection, combination antifungal therapy has been used for severe invasive candida infection, however, there is no good evidence for additional benefit (Hatipoglu and Hatipoglu 2013).

**CRYPTOCOCCUS NEOFORMANS INFECTION**

Cryptococcosis due to *Cryptococcus neoformans* is a systemic fungal infection now most commonly seen in adults with advanced HIV disease. It is rarely seen in HIV-infected children, and following glucocorticoid therapy or solid organ transplant (Severo et al. 2009). CNS involvement is the most serious complication and spread is usually haematogenous from the lungs. The organism produces a granulomatous arachnoiditis that may cause hydrocephalus, cranial nerve palsies and vasculitis of large vessels. The disease may very rarely occur in previously well children (Tjia et al. 1985). Presenting symptoms include headache and fever. The diagnosis of cryptococcosis is difficult, especially in immunosuppressed patients. Blood cultures as well as CSF cultures should be undertaken. The CSF usually shows moderate lymphocytic pleocytosis, increased protein and low glucose. India ink staining demonstrates yeasts in only 60% of patients with positive culture. The test may be positive in up to 90% of cases of cryptococcal meningitis (Siberry et al. 2013). The CSF may be normal in some cases; hence the need to repeat lumbar puncture and to culture large amounts of fluid. Neuroimaging may show cerebral oedema, hydrocephalus and occasionally mass lesions (Fujita et al. 1981). Repeated lumbar puncture may be required to reduce ICP during the acute phase. However, some patients will require shunting. Untreated CNS cryptococcosis is usually fatal. Sequelae in late-treated cases may include blindness,
deafness and chronic hydrocephalus. Treatment practices are
guided by evidence from studies in adults. Antifungal combi-
nation treatment initially with amphotericin B and flucytosine
has been demonstrated to be most effective and is currently rec-
commended (Brouwer et al. 2004; Perfect et al. 2010; Hatipoglu
and Hatipoglu 2013); subsequent prophylaxis to prevent remis-
sion is advised with fluconazole where there is ongoing immu-
nosuppression (Bicanic and Harrison 2004; Perfect et al. 2010).
Cryptococcal meningitis in the context of severe immunosup-
pression secondary to HIV infection may contribute to clinical
deterioration following initiation of antiretroviral therapy. This
is caused by an immune reconstitution inflammatory syndrome
(IRIS). Evidence supports the practice of initiating antifungal
treatments prior to commencing antiretroviral therapy to mini-
mise the risk of this occurring (Siberry et al. 2013).

C. gattii is a rare cause of cryptococcal meningitis and is
found most commonly in tropical and subtropical regions.
In contrast to C. neoformans it is more frequently isolated in
immune competent children (Chen et al. 2014).

OTHER MYCOTIC INFECTIONS

Mucormycosis (or Zygomycosis) is a rare fungal infection by
environmental moulds from the order Mucorales that usually
infests the sinuses and in the immunocompromised may pen-
etrates locally into surrounding tissues including the eye and
brain. Combined infections with Aspergillus may also occur.
Local surgical treatment as well as antifungal therapy may
be required. Voriconazole resistance is common. Liposomal
amphotericin B is recommended as first-line therapy. Recent
evidence suggests that posaconazole may also be an additional
effective therapy but evidence is limited (Rogers and Frost
2009; Blyth et al. 2014).

CNS infections caused by Coccidioides immitis, Histoplasma
capsulatum or Blastomyces dermatitidis are rare in
western Europe. These fungal infections are common in
some regions of the Americas, Africa and Asia. CNS infec-
tion usually occurs as part of a disseminated infection in the
immunocompromised and usually with pulmonary manifes-
tations. Clinical features include headaches, low-grade fever,
weight loss and minimal meningeal signs. Hydrocephalus
may occur. The diagnosis is suggested by the presence of
pulmonary lesions, which may remain quiescent for many
years. Liposomal amphotericin is probably the most effective
treatment (Wheat et al. 2005; Panicker et al. 2006; Siberry et al.
2013).

Scedosporium apiospermum is a fungus found in the soil and
contaminated water. CNS scedosporium infection is usually
associated with severe immunosuppression (Blyth et al. 2014)
but has also been reported in paediatric cases of near drowning
(Kratagkou et al. 2007). Scedosporium spp. are often resistant
to first-line antifungal agents. Treatment should therefore be
guided by expert advice and in vitro sensitivity data (Blyth
et al. 2014).

Many other rare forms of fungal infection may occur, and
should be considered in the immunocompromised with poor
phagocytic function. Expert advice should be sought for
treatment and management. Often a combined surgical and drug
treatment may be required, especially if there is abscess formation.

### PROTOZOAN AND PARASITIC INFESTATION OF THE CNS

With the exception of toxoplasmosis and, to a certain extent,
neurocysticercosis, protozoan or parasitic involvement of
the CNS is rare in developed countries. Malaria is, however,
of increasing importance because mass travel to endemic
countries has developed enormously and because preventive
prevention is not always taken or effective. Table 11.16 lists
the main clinical features and available treatments for some
protozoan and parasitic diseases.

#### MALARIA

Malaria is a tropical parasitic disease of red blood cells, trans-
mitted by the Anopheles mosquito, of which five species
infect humans (P. vivax, P. falciparum, P. malariae, P. ovale
and P. knowlesi). In non- endemic countries such as the UK,
case fatality is around 1% but increases in the elderly (Smith
et al. 2008; Mali et al. 2012). In endemic areas, such as parts
of Africa, mortality is highest in young children, and at least
1 million children are estimated to die from malaria annually
in Africa alone (Snow et al. 2005). Cerebral involvement, a
severe complication of malaria most often caused by P. falcipa-
rum is a major cause of death, with the peak incidence of
cerebral malaria in children aged between 2 and 6 years. Cere-
bral malaria in children is defined by three criteria: disturbances
of consciousness with inability to localise pain (Blantyre coma
score <3/5) more than 1 hour after a seizure; presence of para-
sitaemia; and absence of other causes of encephalopathy. The
histopathological hallmark is engorgement of the cerebral cap-
illaries and venules with parasitised and non-parasitised red
blood cells (MacPherson et al. 1985). The earliest symptom
is usually fever, followed by signs of respiratory distress (sec-
ondary to metabolic acidosis and/or anaemia), convulsions and
a decreased level of consciousness. Movement disorders and
abnormal postures are common. Seizures, which may occur
in any form of malaria, are common, and can be generalised
or focal. Some may be subclinical. They are associated with a
poorer outcome, particularly if prolonged. Status epilepticus is
present in 10–20% of cases. Hypoglycaemia is present in 30% of
patients and is of severe prognostic significance (Molyneux
et al. 1989). Raised ICP is present in most children (Newton
Table 11.16  Some protozoan and parasitic infestations of the CNS, and possible treatment options

<table>
<thead>
<tr>
<th>Disease (organism)</th>
<th>Main clinical features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>African trypanosomiasis (T. gambiense or T. rhodesiense)</td>
<td>Convulsions, disturbed consciousness, sometimes focal deficits (hemiplegia), spastic diplegia, choroothaeritis</td>
<td>Stage 1 – pentamidine (T. gambiense) suramin (T. rhodesiense) Stage 2 – eflornithine melarsoprol, melarsoprol–nifurtimox combination</td>
</tr>
<tr>
<td>Amoebiasis (Naegleria fowleri)</td>
<td>Meningoencephalitis</td>
<td>Amphotericin B, miconazole and rifampicin</td>
</tr>
<tr>
<td>Amoebiasis (Entamoeba histolytica)</td>
<td>Brain abscess secondary to hepatic and pulmonary involvement</td>
<td>Metronidazole, tinidazole</td>
</tr>
<tr>
<td>Echinococcus</td>
<td>Raised intracranial pressure, focal deficits</td>
<td>Albendazole ± corticosteroid</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>Encephalopathy, seizures, fever</td>
<td>Artesunate, quinidine, quinine</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>Seizures, encephalopathy</td>
<td>Albendazole, praziquantel ± corticosteroids</td>
</tr>
<tr>
<td>Schistosomiasis (S. japonicum, S. mansoni, S. haematobium)</td>
<td>Transverse myelitis, granuloma of spinal cord, radiculitis, encephalopathy</td>
<td>Praziquantel, oxamnique ± corticosteroids</td>
</tr>
<tr>
<td>Trichinosis (T. spiralis)</td>
<td>Fever, myalgia, encephalopathy, focal signs, papilloedema</td>
<td>Mebendazole/ albendazole/ albendazole ± corticosteroids</td>
</tr>
<tr>
<td>Visceral larva migrans (Toxocara canis or T. catti)</td>
<td>Encephalopathy, seizures, optic neuritis, myelitis</td>
<td>Mebendazole, albendazole, mebendazole/ albendazole ± corticosteroids</td>
</tr>
</tbody>
</table>

Adapted from Abramowicz (2004) and with reference to AAP (2012), Simarro et al. (2012) and Lurje et al. (2010).

et al. 1991) with cerebral malaria, and is thought to be due to increased cerebral blood volume. Those children with a markedly elevated ICP have a higher mortality, and greater incidence of long-term sequelae.

Diagnosis is generally made on history, clinical examination, and examination of thick and thin blood smears. Rapid tests for falciparum malaria have a specificity and sensitivity above 97% (Abba et al. 2011) but are not as good as an experienced microbiologist’s confirmation. The CSF findings are usually unremarkable, and if pleocytosis is seen on CSF, meningoencephalitis becomes a more likely diagnosis. Treatment should be started without definite proof in case of meningitis or encephalitis becomes a more likely diagnosis.

**ACQUIRED TOXOPLASMOSIS**

Infection with Toxoplasma gondii is usually mild or asymptomatic, but the CNS can be infected, causing meningoencephalitis in an immunocompetent host, encephalitis and chorioretinitis in neonates following transplacental infection, chorioretinitis as a primary infection, or intracerebral mass lesions in the immunocompromised host.

**NEUROCYSTICERCOSIS**

Neurocysticercosis (NCC) is the most common helminthic disease of the CNS and in many developing countries a leading cause of acquired epilepsy. The disease results from poor sanitation, when humans become the intermediate host in the life cycle of Taenia solium by ingesting the eggs of the tapeworm. Infestation by the encysted form of T. solium may then occur within brain parenchyma, the basilar cisterns or rarely
the spinal cord, causing inflammation, oedema and residual calcification. Neurocysticercosis usually presents in children when cysts start dying, and provoke inflammation. They present usually with prolonged focal or generalised seizures, but occasionally with focal deficits, signs of raised ICP secondary to cysticercotic encephalitis or hydrocephalus (from blockage of the ventricular system by cysts), or even cognitive decline. NCC is thought to be the most common cause of acquired epilepsy in endemic regions. Diagnosis is made by demonstrating either a single ring-enhancing lesion with surrounding oedema on CT scan or by seeing multiple lesions, some of which may be calcified. MRI may reveal a scolex (Fig. 11.24a) or multiple lesions (Fig. 11.24b) MRI may reveal a scolex which is pathognomonic. Differentiation of a single lesion from other single granulomata, such as a tuberculoma, is difficult, but clinical data taken together with neuroimaging and immunological tests can help confirm the diagnosis. Del Brutto et al. (2001) have proposed a set of diagnostic criteria for neurocysticercosis to aid in diagnosis. Treatment with albendazole (15mg/kg/day for 8 days) has proved effective and superior to praziquantel (Sotelo et al. 1990), with steroids added in cases of heavy infestation or when side effects develop with treatment. A meta-analysis has also shown that the use of albendazole appears to decrease the long-term risk of seizures (Del Brutto et al. 2006).
ECHINOCOCCOSIS

Human infestation by the dog tapeworm, Echinococcus granulosus, is known as hydatid disease and is common in sheep-raising countries. Humans are infected by ingesting the ova shed by dogs (the definitive hosts). E. granulosus causes cystic hydatid disease, and is mainly responsible for liver and lung hydatids, although in 5% cysts develop in the CNS. As the cysts are slow-growing, they frequently remain asymptomatic until they reach considerable dimensions. Clinical features are mainly symptoms and signs of intracranial hypertension, while focal neurological deficits are rare. On CT or MRI, the cysts appear as round or oval masses with a smooth border and a content of CSF density (Fig. 11.25). Midline shift and ventricular distortion may occur (Tüzun et al. 2002). ELISA or indirect haemagglutination for echinococcal antigens may be helpful.

EOSINOPHILIC MENINGITIS

Parasitic or protozoan diseases are the most common cause of eosinophilic meningitis. However, a high proportion of eosinophilic cells (>4%) may also be present in cases of infectious or post-infectious meningitis secondary to fungal, rickettsial, mycoplasmal or treponemal disease, SSPE and lymphocytic choriomeningitis. CSF eosinophilia can also be associated with noninfectious disorders, such as Hodgkin disease, multiple sclerosis, leukaemia, subarachnoid haemorrhage and reaction to intrathecal antibiotics (Weller 1993).

TETANUS

Tetanus is a serious vaccine-preventable infection that, although rare in industrialised countries, is common in the developing world is still common in the developing world with neonatal tetanus accounting for over half the cases. Vaccine strategies have resulted in a significant reduction of cases, but still the WHO estimates that in 2015, 34 000 neonates died from neonatal tetanus (WHO 2017). Umbilical cord infections and penetrating wounds contaminated with dirt, faeces and saliva are at high risk for introduction of spores of Clostridium tetani. These spores germinate and multiply, and tetanus results from the action of the soluble exotoxin produced, tetanospasmin, which binds to specific receptors on the neuronal cell membrane. It is taken up by nerve terminals and is transported via retrograde axonal transport to the corresponding cell bodies and surrounding presynaptic terminals. The toxin prevents the release of inhibitory neurotransmitters from the presynaptic terminals thus producing uncontrolled firing, with consequent muscle spasms. The clinical manifestations are due to both the central and peripheral actions of the toxin on the release of acetylcholine at the motor plate. Symptoms appear between 3 and 21 days after injury. Shorter incubations are associated with the most severe forms and neonatal tetanus (3–14 days). There are four types of tetanus: generalised, localised, cephalic and neonatal. The first manifestation of tetanus is usually trismus, often associated with neck and back stiffness, salivary stasis and dysphagia. Retraction of the angles of the mouth results in the classic ‘risus sardonicus’ appearance. Subsequently, rigidity becomes generalised and tetanic spasms develop, often precipitated by sensory stimuli. Consciousness is preserved. Sudden respiratory failure due to prolonged spasms, airway blockage or bronchopneumonia accounts for most fatalities. In some cases, tetanus remains localised around the infected wound, in the form of a spasm limited to neighbouring muscles. Cephalic tetanus is consecutive to C. tetani otitis or a facial wound. Some degree of trismus is present. Often facial palsy and occasionally paralysis of other cranial nerves are seen. All forms of localised tetanus may secondarily become generalised. Neonatal tetanus follows infection of the umbilical stump in infants of unimmunised mothers. Infants present with weakness and inability to suck, usually in the second week of life. Mortality is high, and developmental delay common in survivors. Diagnosis is clinical, with isolation of C. tetani successful in only 30% of cases, and no responsible wound apparent in 7–30% (Crone and Reder 1992). Treatment of tetanus demands intensive care for the maintenance of a free airway and adequate ventilation. The use of sedatives, especially benzodiazepines, is helpful. If adequate ventilation cannot be maintained because of the spasms, neuromuscular blockade is indicated. At the same time, antibiotic treatment (usually with high-dose penicillin G) is given to eradicate the organisms, and neutralisation of any as yet unbound toxin is achieved with antitoxin. Despite such measures, the mortality of tetanus is high, but in those who survive, recovery although slow is often complete. The best prophylaxis of tetanus is immunisation with tetanus toxoid. However, severe tetanus may occur in immunised patients.

DIPHTHERIA

Diphtheria is a rare disease in developed countries. It is caused by a Gram-positive, aerobic bacillus Corynebacterium diphtheriae, which, following a throat infection, produces a toxin that blocks the incorporation of amino acids into polypeptide chains and inhibits protein synthesis, resulting in tissue destruction and membrane formation.

Neurological manifestations present as one of two forms: local paralyses and polyneuropathy. Local paralyses appear three weeks after throat infection and consist primarily of paralysis of the soft palate and paralysis of accommodation.
Oculomotor and pharyngeal paralyses are possible. One to two weeks later, a symmetrical generalised sensorimotor polyneuropathy occurs with abolition of the deep tendon reflexes. Deep sensation is more involved than motor functions because the toxin induces a segmental demyelination that predominates on the posterior roots (Solders et al. 1989). Cardiac involvement may occur and the neurological picture may closely resemble the GBS. The course is usually toward complete spontaneous cure. Diagnosis is clinical, although culture of the bacillus from a throat swab is possible. Treatment is with diphtheria antitoxin, although this will only neutralise unbound toxin, and antibiotics (penicillin or erythromycin). There is no specific treatment of diphtheritic paralyses apart from supportive measures. Mortality is around 5–10%, although higher in the young and elderly. Recovery is normally complete.

BOTULISM

Botulism is caused by the powerful neurotoxin produced by the spore-forming bacterium Clostridium botulinum. The botulinum neurotoxin causes paralysis of peripheral nerve terminals by inactivating neurotransmitter release. There are six phylogenetically distinct clostridia which produce seven different botulinum neurotoxin serotypes (A–G), four of which (A, B, E and F) cause naturally occurring human botulism (Rossetto et al. 2014). There may be an eighth serotype (H), but this still requires experimental validation (Dover et al. 2014). Five forms of botulism occur and they are classified according to the route of entry of toxin. The most common type (food botulism) is due to ingestion of the preformed toxin in improperly sterilised preserves or canned foods. In infantile botulism, however, type C. botulinum spores are ingested and produce neurotoxin in the digestive tract. This is then absorbed through the intestinal wall producing systemic effects. Less common is wound botulism, where the toxin is produced as a result of a wound infection by C. botulinum. This has recently become more frequent as a result of HIV infection and intravenous drug abuse. The fourth type is adult enteric botulism, and the fifth is inhalational, from botulinum toxin being used as a biological weapon.

Patients present with cranial nerve paralyses, causing symptoms such as diplopia, dilated pupils unreactive to light and blurring of vision as a result of paralysis of the ciliary muscles, dysphagia and dysphagia. As the disease progresses in a descending manner, diffuse paralysis with areflexia and respiratory difficulties develops. Autonomic involvement produces dryness of the mucous membranes and bladder distension. Such signs in the presence of fully preserved consciousness are highly characteristic. In food-borne botulism, symptoms can appear within hours of ingestion of contaminated food; gastrointestinal symptoms are common, with abdominal pain, diarrhoea and vomiting. Wound botulism presents as above without the gastrointestinal manifestations. Infantile botulism can occur at any time during the first year of life, but in the majority of cases occurs before the age of 6 months. It frequently follows the introduction of solid food in breast-fed infants, and ingestion of honey may be a risk factor. It is characterised by a prodromal phase of constipation with progressive development over 4–5 days of the complete picture of hypotonia, areflexia, poor sucking, prosis and paralysis of other cranial nerves and of the limbs (Thompson et al. 1980; Schreiner et al. 1991). Respiratory difficulty is frequent, and ventilatory support is necessary for most patients. Administration of aminoglycoside antibiotics may precipitate respiratory difficulties (L’Hommedieu et al. 1979; Long et al. 1985). A mild form may be marked only by hypotonia and poor feeding (Thompson et al. 1980). Moreover, asymptomatic carriers are known to exist. It is thus difficult to attribute other syndromes, such as sudden infant death syndrome, to botulism on the sole basis of isolation of C. botulinum from the stools (Sonnabend et al. 1985).

The diagnosis of botulism is made clinically, with neurological symptoms resulting from the blockade at neuromuscular junction. Routine laboratory tests including CSF are usually normal, and the diagnosis is made by demonstration of the toxin in the blood or of the organism in the stool. EMG can be helpful to exclude other pathologies. It shows brief, low-amplitude potentials and an incremental response to fast (25–30Hz) repetitive nerve stimulation characteristic of a presynaptic block (Gutierrez et al. 1994). The response to slow (2–5Hz) stimulation is more variable, with increased, normal or decreased responses (Cornblath et al. 1983). Differential diagnoses include neonatal myasthenia, sepsis, viral CNS infections and various other causes of disordered neuromuscular transmission (Swift 1981).

Treatment involves early (within 7 days) administration of botulinum immunoglobulin (BIG), to prevent progression of the illness, plus both respiratory and nutritional supportive care (Haffen 2006). Recovery takes place over a period of several weeks but some weakness may persist for months to years. Relapses may occur (Glauser et al. 1990). It is of note that large quantities of toxin are secreted for months but tolerance develops for unknown reasons.

OTHER TOXIN MEDIATED DISORDERS

Some other bacterial infections may act on the CNS through neurotoxins. Shigella infection is associated with a higher incidence of convulsions than explained by associated fever (Ashkenazi et al. 1987). Infection by E. coli O157:H7 seems to be a frequent cause of the haemolytic uraemic syndrome (Boyce et al. 1995).

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Chapter 11 Infectious Diseases


Parainfectious and Other Inflammatory Disorders of Immunological Origin

Marc Tardieu and Michael Johnston

Acute Demyelinating Syndromes
- Acute Demyelinating Encephalomyelitis
- Optic Neuritis
- Acute Transverse Myelitis
- Brainstem Encephalitis

Multiple Sclerosis
- Cerebrospinal Fluid in Multiple Sclerosis
- Multiple Sclerosis and Cognitive Development in Children
- Clinically Isolated Syndromes
- ADEM versus Multiple Sclerosis
- Therapy for Paediatric Multiple Sclerosis

Antibody-Mediated Encephalopathy
- Neuromyelitis Optica
- Anti-Myelin Oligodendrocyte Glycoprotein Encephalitis
- Anti-Glutamate Receptor Encephalopathies and Related Diseases
- Streptococcal Infection-Related Disorders
- Hashimoto Encephalopathy and Anti-Thyroperoxidase Antibodies

Inflammatory Diseases of the White Matter that Mimic Multiple Sclerosis and Related Disorders
- Clues to the Differential Diagnosis of White Matter Inflammatory Diseases

Vasculitis
- Common features of primary and secondary cerebral vasculitis
- Characteristics of the different brain vasculitides

Main Syndromes with Secondary Cerebral Vasculitis
- Systemic Lupus Erythematosus
- Behcet Disease
- Primary Central Nervous System Vasculitis

Immunogenetic Diseases Mimicking Multiple Sclerosis and Related Disorders

Tumours Mimicking Multiple Sclerosis

Other Genetic Diseases Mimicking Inflammatory White Matter Diseases

Other Inflammatory Diseases of the Central Nervous System
- Granulomatous Disorders of the Central Nervous System and Related Disorders
  - Sarcoidosis
  - Polyarteritis Nodosa

Auto-Inflammatory Disorders with Neurological Involvement
- Neonatal onset multisystem inflammatory disease (NOMID) or Chronic inflammatory neurological cutaneous articular syndrome (CINCA)
- SUSAC syndrome
Cerebellitis 689
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  Opsoclonus-Myoclonus Syndrome (Dancing Eye syndrome, Kinsbourne's syndrome) 692
  Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation 692
Immune mediated and inflammatory disorders taken together are relatively common in paediatric neurology practice as children are more likely than adults to encounter infectious diseases and immunisations (Chitnis et al. 2016). A variety of disorders are considered in this category including demyelinating conditions such as acute disseminated encephalomyelitis (ADEM), multiple sclerosis, optic neuritis and transverse myelitis as well as other inflammatory disorders of white matter including vasculitis, infections, and granulomatous disorders (Table 12.1). Acute auto-antibody mediated disorders such as anti-N-methyl-D-aspartate (NMDA) receptor mediated encephalopathy, tumours such as Langerhans cell histiocytosis and genetic disorders including Aicardi-Goutières syndrome as well as some mitochondrial diseases are also included under this category, making it one of the most challenging areas of neurology. Many of these disorders are self-limited and reflect a brief encounter with a new infection but at other times the first episode of a more chronic disorder such as multiple sclerosis. In this section we discuss these disorders as well as some information that can be used to provide prognosis of future events and therapy.

**Table 12.1 Major inflammatory diseases of the white matter and conditions that mimic them**

<table>
<thead>
<tr>
<th>Multiple sclerosis (MS) and related disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>Clinically isolated syndromes (CIS): optic neuritis, transverse myelitis, brainstem-related syndromes, polyfocal clinically isolated syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other inflammatory diseases of the white matter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Autoinflammatory disorders with neurological involvement (CINCA and cryopyrin-associated periodic syndromes)</td>
</tr>
<tr>
<td>Acute encephalopathies with autoantibodies (anti-glutamate receptors antibody-mediated encephalopathies, Hashimoto’s encephalopathy, Streptococcus-related disorders)</td>
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<th>Tumours mimicking multiple sclerosis</th>
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<td>Primary cerebral lymphoma</td>
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<th>Genetic diseases mimicking multiple sclerosis and related disorders</th>
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<td>Aicardi-Goutières syndromes and disease of the RNA metabolism</td>
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MOG, myelin oligodendrocyte glycoprotein; CINCA, chronic infantile neurologic cutaneous articular syndrome; ANCA, anti-neutrophil cytoplasmic antibodies; X-ALD, X-linked adrenoleukodystrophy.

**ACUTE DEMYELINATING SYNDROMES**

Several disorders referred to as acute demyelinating syndromes (ADS) are responsible for episodes of nervous system dysfunction due to immune mediated disruption of myelin in the central nervous system (CNS) in children (Rotay et al. 2006). A recent Canadian study (Banwell et al. 2009) of 200 children, 1–18 years of age presenting with ADS found the most common presentations of ADS were optic neuritis (23%), ADEM (22%) and transverse myelitis (22%). Children with ADEM were more likely to be younger than 10 years while children with mono-lesional ADS such as optic neuritis and transverse myelitis were more likely to be older than 10 years. ADEM differs from other version of ADS because it includes encephalopathy (Table 12.2): there were 73 incidents per year in the study leading to an annual incidence of 0.9 per 100 000 children while a family history of multiple sclerosis was reported in 8%. Various versions of ADS can also be described as clinically isolated syndromes (CIS), which can be the harbingers of multiple sclerosis or single episodes that do not progress to meet the criteria for multiple sclerosis of two or more events disseminated in time by 4 or more weeks (Waldman et al. 2014). CIS episodes include unilateral optic neuritis, ataxia, cerebellar tremor, cortical motor or sensory impairment lasting at least 24 hours that are linked to episodes of demyelination.
without encephalopathy. Episodes may be unifocal or multifocal when there are lesions in more than one location. A Dutch study of ADS (Ketelslegers et al. 2012) in children reported an incidence of 0.66/100,000 per year and most patients presented with polyfocal ADS without encephalopathy (30%) followed by polyfocal ADS with encephalopathy (24%), optic neuritis (22%), monofocal ADS (16%), transverse myelitis (3%) and neuromyelitis optica (3%). Familial autoimmune diseases were reported in 46% of children with relapsing disease compared to 15% with monophasic disease. During the study period of 4 years 23% of children were diagnosed with multiple sclerosis.

**ACUTE DEMYELINATING ENCEPHALOMYELITIS**

Acute demyelinating encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating disorder of the nervous system that produces a prominent encephalopathy, is more common in children than in adults and thought to be triggered by infectious diseases or vaccinations (Tenembaum et al. 2007; Pohl et al. 2016). Two forms of ADEM have been defined, the classic monophasic form, recurrent ADEM and multiphasic ADEM which is a relapse with new features (Table 12.1). According to the International Paediatric Multiple Sclerosis Study Group criteria (IPMSSG; Table 12.2) modified in 2013 (Waldman et al. 2014), monophasic ADEM is characterised by a first polyfocal event affecting the CNS associated with an alteration in consciousness not due to another systemic illness and associated with poorly demarcated white matter lesions as well as lesions in the thalamus, basal ganglia, deep grey matter or spinal cord. It is a relatively rare disorder with an incidence in the United States and Canada of about 0.3/100,000 population. The incidence is higher in the winter and spring months in both the United States and United Kingdom consistent with link to infections. Historically ADEM occurred with an incidence of 1:1,000 after infection with measles and 1:10,000 after varicella zoster or rubella virus, but the incidence associated with these illnesses has fallen dramatically where vaccination for these diseases is widespread (Tenembaum et al. 2007). The incidence was also relatively high after vaccination with Pasteur’s rabies vaccine and smallpox vaccination but it has fallen as these vaccines have improved. The presentation of ADEM can resemble other inflammatory disorders of the nervous system as shown in Table 12.1 and it has been reported as a rare presentation of human immunodeficiency virus (HIV) infection in children (Patra et al. 2014). A typical patient with ADEM is under 10 years of age and develops an infectious illness followed in a few days by fever, malaise and headache, nausea as well as vomiting and then by drowsiness, confusion and seizures (Tenembaum et al. 2002). Examination usually shows specific focal neurological signs including bilateral up-going toes, increased reflexes, cranial nerve palsies and optic neuritis which is often bilateral, meningeal signs and slurred speech or aphasia, hemiparesis and ataxia. Signs of spinal cord impairment or polyradiculoneuropathy can also occur as well as prolonged seizures or status epilepticus. Examination of cerebrospinal fluid (CSF) is important to rule out treatable bacterial or other CSF infections but is generally performed after the MRI to rule out mass lesions and increased intracranial pressure (Table 12.1). The CSF in ADEM often shows pleocytosis and oligogocional bands and the EEG slowing consistent with encephalopathy.

Neuroimaging with magnetic resonance imaging (MRI) plays an important role in the diagnosis of ADEM usually associated with prominent asymmetrical bilateral T2 and fluid inversion recovery (FLAIR) enhancing lesions that reflect pathology in myelin as well as areas of restricted diffusion that may reflect vasogenic oedema (Fig. 12.1). Scattered enhancing lesions also appear in subcortical and cortical grey matter and in the spinal cord in ADEM which may also show prominent enhancement with gadolinium. Pathologically these lesions correspond to infiltrates of T-cells and macrophages associated with demyelination. MRI is important for distinguishing ADEM from the first attack of multiple sclerosis and other disorders. Although 45% of all children with an initial demyelinating episode will have a second episode, only 20% of children initially diagnosed with ADEM will later be diagnosed with multiple sclerosis (Yeh and Tardieu 2010). Ketelslegers et al. (2010) compared diagnostic criteria for distinguishing multiple sclerosis from ADEM (Mikaeloff et al. 2004a, b, 2007) and confirmed the newer criteria recommended by Callen et al. (2009) who reported that periventricular lesions are more frequent in children with multiple sclerosis compared to ADEM. The presence of ≥2 periventricular lesions, black holes and/or a lesion distribution that was not diffusely bilateral on T2-weighted images made multiple sclerosis more likely to be present than ADEM.

Experimental autoimmune encephalomyelitis (EAE) has been reported to be a model for ADEM and cross-reactive
T cell responses have been demonstrated between viral sequences and myelin basic protein (Javed and Khan 2014). Several characteristic imaging patterns of cerebral involvement have been described including scattered small lesions, large confluent lesions, symmetrical bi-thalamic involvement and hemorrhagic lesions. The latter finding may indicate acute hemorrhagic leukoencephalitis (AHL) which is a more fulminant and aggressive form of ADEM with a higher mortality (Kuperan et al. 2003). Patients with AHL may have perilesional oedema and severe increased intracranial pressure with magnetic resonance spectroscopy showing low levels of N-acetylaspartate (NAA), a marker for mitochondria in neurons, as well as elevated lactate in regions of prolonged T2 signal (Aydin et al. 2010). AHL has been reported following a variety of viruses including the H1N1 strain of influenza as well as enterovirus infections and it has also been observed in patients following diphtheria, tetanus toxoid and pertussis vaccinations. The disorder has also occurred in patients with mutations in the complement factor I pathway as well as in three sibling infants in a family in Tunisia with genetic mutations in the RANBP2 gene (Broderic et al. 2013; Jeganathan et al. 2013; Tabarki et al. 2013; Di Meglio et al. 2014).

The clinical presentation of patients with ADEM is often alarming and patients are usually admitted to intensive care units. However, despite the nature of their presentation children with ADEM are very likely to recover with few neurological deficits and MRI lesions in the brain often disappear as well (Tenembaum 2013), with full recovery seen in 50–70% of patients and 20–30% recovering with some minor residual disability: average time to recover is 1–6 months. However the mortality rate may be as high as 5% and there may be milder neurocognitive deficits even in children who appear to have a full neuromotor recovery (Suppiej et al. 2014).

The IPMSSG consensus definitions for ADEM require that it must be multifocal, polysymptomatic and include encephalopathy (as an essential requirement). An alternative diagnosis for a first acute inflammatory event is ‘clinically isolated syndrome’ (CIS), with a CIS event being either monofocal (such as isolated optic neuritis) or multifocal but cannot include encephalopathy. As with adults, children with two or more discrete demyelinating events separated in time and space meet criteria for multiple sclerosis; in children with multiple sclerosis the demyelination events must not meet ADEM criteria. To test the usefulness of these new criteria a new cohort of 40 patients (18 males, 22 females; mean age 8 years [SD 4 years 4 months]) with CNS demyelination were studied. Using IPMSSG definitions the presenting diagnosis was ADEM in 12 patients and CIS in 28 patients and at
presentation patients with CIS were more likely to have intrathecal synthesis of oligoclonal bands and fulfill KIDMUS multiple sclerosis MRI criteria, compared with patients with ADEM (\( P < 0.025 \)).

 Patients were followed-up for a mean of 2 years and 2 months with only one of 12 patients with ADEM going on to develop multiple sclerosis during the study period while 13 of 28 patients with CIS relapsed and fulfilled a diagnosis of multiple sclerosis (\( P < 0.025 \)).

 The proportion of children with ADEM subsequently diagnosed with multiple sclerosis within 5 years varies between 10% and 18% (Waldman et al. 2014). The methodology of the study has an impact on this proportion: when the criterion of encephalopathy in ADEM definition is strictly applied the percentage of children with ADEM who subsequently are diagnosed with multiple sclerosis becomes lower (an absence of encephalopathy at first demyelinating event is a well-defined risk factor for relapse); however, the region of study might also be a factor. In any case this proportion is lower than that of children with any type of first demyelinating event subsequently diagnosed with multiple sclerosis, the percentage being between 18% and 46% depending on studies and methodology (Mikaeloff et al. 2004b, 2007). Dale and Pillai (2007) followed groups of children with ADEM, multiphasic disseminated encephalitis (MDEM) and multiple sclerosis for approximately 5 years and reported that subcortical white matter lesions were common in both groups although periventricular lesions were more common in multiple sclerosis. In contrast, in ADEM there was relative periventricular sparing and MRI follow-up revealed complete or partial lesion resolution in 90% as well as no new lesions while all multiple sclerosis patients had new lesions at follow-up. Female sex and age greater than 11 years are associated with a greater risk of multiple sclerosis after ADEM while a normal brain MRI is associated with a lower risk. Absence of non-enhancing T1 hypointense lesions and less than 2 periventricular lesions at onset favour ADEM while periventricular T2 lesions and more than one hypointense T1 lesions favour multiple sclerosis. A United States study of ADEM and multiple sclerosis diagnosed in children after long term follow-up found that none of the patients who presented with encephalopathy developed multiple sclerosis (Alper et al. 2009). Family history of multiple sclerosis is also more common in children with multiple sclerosis over ADEM while the multiphasic form of ADEM comprises 5% or less of children, most of whom develop multiple sclerosis.

 Therapy for ADEM is generally started with high dose steroids such as intravenous methylprednisolone (10–30mg/kg/day to a maximum of 1 gram per day) followed by a steroid taper of prednisone over 4–6 weeks. Some data suggests that the outcome of ADEM is improved by steroids but there are no large controlled trials, while IgG and plasma exchange have also been used. Dale et al. (2000) reported that 20% of 35 children in their series who presented with ADEM relapsed and were classified as having multiphasic disseminated encephalomyelitis (MDEM). These patients generally relapse with signs similar to the original event and may respond to repetition of the same therapy.

**OPTIC NEURITIS**

Optic neuritis presents with sudden onset of diminished vision in one or both eyes due to inflammation of the optic nerve. It can present with swelling of the optic nerve head and a relative afferent pupil defect as well as visual field restriction and painful eye movements. Retrolubular optic neuritis is diagnosed when there are typical signs and symptoms of optic neuritis without optic nerve head swelling. A new technique called retinal optical coherence tomography can assess damage to the retinal fiber layer caused by optic neuritis (Balk and Petzold 2014). Optic neuritis can be caused by multiple sclerosis as well as a variety of other disorders including viral and bacterial infections, viral encephalitis, Lyme disease, sarcoid, cat scratch fever, sinusitis, vaccinations, inherited white matter disorders, B12 deficiency, vasculitis and diabetes, as well as some medications (Toosy et al. 2014). Autoimmune disorders such as systemic lupus erythematosus (SLE) and Sjögren syndrome can also cause optic neuritis while neuromyelitis optica generally causes bilateral optic neuritis in association with transverse myelitis and is associated with antibodies to aquaporin-4 (Wingerchuk and Weinschenker 2014). Optic neuritis is generally associated with better recovery in children than in adults (Brady et al. 1999) with a recent study of paediatric patients with a median age of 11 years with their first episode of optic neuritis showing that 77% regained normal visual function within 1 year although 34% developed signs of multiple sclerosis or neuromyelitis optica (Absoud et al. 2011). The presence of white matter lesions and oligoclonal bands in CSF on an MRI at the time of diagnosis of optic neuritis as well as older age substantially increased the risk of having multiple sclerosis diagnosed (Bonhomme et al. 2009; Heussinger et al. 2013). Another study of optic neuritis in children by Wilejto et al. (2006) reported that optic neuritis was associated with a risk of diagnosis of multiple sclerosis within 2 years in 36% of patients and bilateral optic neuritis carried a greater risk of later multiple sclerosis than unilateral. Clinical findings extrinsic to the visual system on baseline examination and MRI evidence of white matter lesions outside the optic nerves were strongly associated with later diagnosis of multiple sclerosis (Waldman et al. 2011). The randomised, controlled trial of corticosteroids in the treatment of acute optic neuritis in adults found that intravenous methylprednisolone followed by oral prednisone sped up the recovery of vision and resulted in slightly better vision at 6 months but there has been no comparable study in children with optic neuritis (Beck et al. 1992).

**ACUTE TRANSVERSE MYELITIS**

Acute transverse myelitis (ATM) affects one to three per million children per year and is suspected when there is acute...
onset of sensory, motor or autonomic dysfunction attributable to spinal cord dysfunction with a defined sensory level and MRI rules out extra-axial compression but shows gadolinium enhancement (Transverse Myelitis Working Group 2002; Absoud et al. 2011; Ketelslegers et al. 2012). According to the Transverse Myelitis Consortium Working Group diagnosis guidelines, the diagnosis of transverse myelitis is also supported by pleocytosis, oligoclonal bands or elevated IgG index in the spinal fluid. However, it is also important to rule out other causes of spinal cord paralysis including arterial stroke, AVM, collagen vascular disorders such as SLE as well as infectious diseases including HIV and herpes (Verhey and Banwell 2013; Sarioglu et al. 2014). Guillain-Barré syndrome (GBS) can also present with ascending numbness, tingling and leg weakness but GBS generally lacks CSF pleocytosis and a definable sensory level or spinal cord lesion on MRI. ATM is usually a monophasic illness and a history of previous episodes of myelopathy, optic neuritis or brain lesions on MRI may suggest multiple sclerosis. Neuromyelitis optica (NMO) should also be suspected with recurrent transverse myelitis, especially if there is concurrent bilateral optic neuritis, involvement of a spinal lesion greater than three vertebral segments on magnetic resonance and/or serum antibodies to aquaporin-4 protein (Absoud et al. 2014). A small number of children with transverse myelitis plus ADEM have also been reported and they present with signs of encephalopathy and central demyelination plus flaccid paralysis as well as electromyographic evidence of axonal loss in nerve roots and worse than average prognosis (DeSena et al. 2014).

ATM in children less than 18 years of age is a relatively rare disorder estimated to account for about 20% of the 1400 individuals diagnosed each year in the United States. One of the largest centre-based follow-up studies of children with ATM by Picard et al. (2007) showed 47 affected individuals of whom 42 were monophasic and idiopathic, with four later diagnosed with NMO, ADEM, SLE or multiple sclerosis. In this cohort there were two distinct groups by age at onset, less than 3 years of age and the other 5–17 years of age with males and females equally affected. Evidence of an infectious disease such as fever or elevated white blood cell count was present on average of 11 days prior to spinal cord symptoms of ATM, while 28% had been given an immunisation or allergy injection within the previous 30 days and antecedent trauma to the child such as a fall was documented in 13%. Almost 90% of children described sensory loss and numbness, weakness, urinary dysfunction and pain at the onset of illness with the same number becoming bed/wheelchair bound and some needing assisted ventilation within 2 days of onset. Gadolinium infusion showed magnetic resonance enhancing lesions in 74% and the CSF white blood cell count was elevated in 50% and protein in 48% but these values were normal in 31% while oligoclonal bands were present in less than 5%. At follow-up, 67% were able to walk or use a manual wheelchair to travel 150 feet and 50% required intermittent bladder catheterisation and experienced persistent numbness and dysesthesias. Older age at onset, shorter time to diagnosis, lack of CSF pleocytosis and fewer spinal cord segments involved were associated with better outcome while hypodensity of the cord on T1-weighted images was associated with worse outcome.

The largest study to date of risk factors for poor outcome following idiopathic transverse myelitis in children is a recent European study of 95 children less than 16 years of age from clinical centres in France and the United Kingdom (Deiva et al. 2015). This study reported that 17% relapsed with a diagnosis of multiple sclerosis in 14% and NMO in 3%. Female sex and the presence of associated brain lesions on MRI were identified as risk factors for relapse using logistic regression analysis. Twenty-eight (30%) of the transverse myelitis group had a poor outcome defined by a Kurtzke Expanded Disability Status Scale (EDSS) score of >4 or an American Spinal Injury Association impairment (ASIA) score of <D. The risk factors linked to poor outcome through logistic regression were female sex (odds ratio: 5.8), severe ASIA scale at onset (odds ratio: 33.5), gadolinium enhancement on spinal MRI (odds ratio: 24.1), absence of pleocytosis (odds ratio: 4.6) and absence of cervical or cervico-thoracic lesions on spinal MRI (odds ratio: 3.9). Another study of prognostic indicators for paediatric acute transverse myelitis reported short time to maximal deficit, long time of peak neurological impairment and initial time of treatment, increased protein levels of CSF and secondary infections were associated with a poor prognosis (Chen et al. 2013) These studies of prognostic factors for relapse and disability are important for planning international collaborative trials to define better therapies and improve outcomes.

Treatment for children with transverse myelitis includes intravenous corticosteroids (70%), intravenous immunoglobulin (33%), oral steroids (28%), plasmapheresis (15%), acyclovir (11%) but there was no discernable difference in outcome in this retrospective study. Sebire et al. (1997) compared a group of patients with transverse myelitis treated with high dose methylprednisolone treatment (1g/1.73m2) for 3–5 days with a historical group of ten patients without steroids and reported the median time to walk independently was significantly reduced from 97 days to 23 days as well as that the proportion of patients with full recovery was 80% versus 10%. Many centres administer intravenous solumedrol 1gr/day intravenous for 3–5 days after ATM is diagnosed which is generally supported by evidence based guidelines (Scott et al. 2011) as is consideration of plasmapheresis or rituximab for immunomodulatory therapy used in adults with the disorder (Bigi and Banwell 2014; Carrithers 2014).

**BRAINSTEM ENCEPHALITIS**

Brainstem encephalitis in children presents as an acute inflammatory process with encephalopathy and prominent signs of brainstem dysfunction including external ophthalmoplegia, ataxia, multiple cranial nerve involvement, tremor, myoclonic jerks as well as swallowing and speech problems (Pavone et al. 2014). As many as half of individuals with ADEM have lesions in the brainstem and present with brainstem signs
and his pupil Pierre Marie reported 13 individuals affected. Multiple sclerosis was first described by Charcot in 1868/1869 and the GQ1b ganglioside antigen characteristic of Miller-Fisher syndrome, while the inflammatory nature of the disorder has been confirmed in several autopsy reports (Paparounas et al. 1999). Similar cases of brainstem encephalitis have been reported after a variety of infections in children and adults including mycoplasma pneumoniae infection, Ebstein-Barr virus, H1N1 influenza, streptococcus and cat scratch fever (Meyer Sauter et al. 2014). Enterovirus 71 emerged in the late 1990s in eastern Asia as a neurovirulent virus that causes large outbreaks of hand-foot-mouth disease, herpangina as well as fever and, in some children, meningoencephalitis, acute flaccid paralysis and brainstem encephalitis complicated by pulmonary oedema and cardiopulmonary collapse. Enterovirus infections in neonates can cause severe disease characterised by meningoencephalitis, myocarditis, pneumonitis and/or hepatitis as well as coagulopathy (Lee et al. 2014). A large number of affected individuals have also been reported after Japanese encephalitis and enterovirus type 71 infection in children associated with complications such as meningitis, poliomyelitis like syndrome and encephalopathy. Some patients with Japanese encephalitis had opsoclonus, gaze palsies, pupillary changes and seizures while an aggressive form of brainstem encephalitis leading to death has been described in a child with an auto-antibody to \( \gamma \)-aminobutyric acid type B receptor (Kruer et al. 2014). Glycine receptor antibodies have also been described in patients with brainstem encephalitis (Carvajal-Gonzalez et al. 2014). Neuroimaging revealed involvement of the brainstem, basal ganglia and hippocampus. Zeng et al. (2012) described MRI changes in children with enterovirus71-induced brainstem encephalitis including lesions in the dorsal pons, medulla, cerebral dentate gyrus, midbrain and thalamus. Treatment of brainstem encephalitis has been successful with intravenous immunoglobulin (Ig) administration and other immunomodulatory therapy including alemtuzumab (Pavone et al. 2014). The effects of steroids are less well documented.

Multiple sclerosis was first described by Charcot in 1868/1869 and his pupil Pierre Marie reported 13 individuals affected by multiple sclerosis with onset in childhood by 1883. Since

<table>
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<th>Table 12.3 Clinical definitions of pediatric multiple sclerosis and related disorders</th>
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<td><strong>Pediatric multiple sclerosis</strong></td>
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<tr>
<td>Two clinical events without encephalopathy consistent with multiple sclerosis separated by more than 30 days and affecting more than one area of the brain, optic nerves or spinal cord. A first clinical event consistent with multiple sclerosis in a patient between 12–18 who fulfills 2010 McDonald MRI dissemination in space in two of four locations, periventricular, juxtaocular, infratentorial or spinal cord, as well as dissemination in time (clinically silent enhancing or non-enhancing on T1-weighted images) criteria on baseline MRI.</td>
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<tr>
<td>One clinical event without encephalopathy typical of multiple sclerosis and MRI demonstrating at least one new T2 lesion on a scan more than 30 days after the incident attack.</td>
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<tr>
<td>An event that fulfills criteria initially for acute disseminated encephalomyelitis followed by a second non-acute disseminated encephalomyelitis event (&gt;3 months from symptom onset) associated with new MRI lesions demonstrated 2010 McDonald disseminated in space criteria.</td>
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<tr>
<td><strong>Pediatric clinically isolated syndrome (all required)</strong></td>
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<tr>
<td>A first monofocal or polyfocal clinical event affecting the central nervous system.</td>
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<td>Encephalopathy is not present (unless transient and caused by fever).</td>
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<tr>
<td>For patients between 12–18 years the 2010 McDonald MRI criteria for dissemination in space and time as applied to the baseline MRI are not met.</td>
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the 1950s paediatric multiple sclerosis has re-emerged as a disease entity (Waldman et al. 2014, 2016; Lee and Chitnis 2016; Tardieu et al. 2016). Paediatric multiple sclerosis in children is typically a chronic remitting, relapsing inflammatory demyelinating disorder in which lesions are disseminated over space and time in the nervous system (Table 12.3). Primary progressive multiple sclerosis is rare in children and should prompt the search for an alternative diagnosis. Estimates in the United States suggest 8000–10 000 children have multiple sclerosis and patients with paediatric multiple sclerosis are thought to comprise 5% of all multiple sclerosis patients throughout the lifespan. A recently estimated incidence of paediatric multiple sclerosis in Germany was 0.64 per 100 000 population with most older than 10 years of age having an incidence of 2.64 per 100 000. Children often experience more frequent relapses than adults especially during the first few years after diagnosis, although overall disease progression may be slower and children experience lethargy and seizures as well as psychological and intellectual decline (Waldman et al. 2014).

Epidemiological data indicates females predominate approximately two to one in children over 10 years of age and that a childhood spent in temperate climates where inadequate exposure to sunlight limits vitamin D increases the risk of paediatric multiple sclerosis (Munger et al. 2014). The fact that multiple sclerosis clusters in some families with large numbers of affected siblings per generation and varies in incidence widely around the world, with some ethnic groups
Chapter 12  Parainfectious and Other Inflammatory Disorders of Immunological Origin

Table 12.4  Diagnostic categories to exclude in childhood multiple sclerosis

<table>
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<th>Category</th>
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<td>Endocrine thyroid disorder, diabetes mellitus</td>
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<td>Inflammatory systemic lupus erythematous, neurosarcoaidosis, antiphospholipid antibody syndrome</td>
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<tr>
<td>Mitochondrial MERFF, MELAS, LHON</td>
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<tr>
<td>Leukodystrophy metachromatic leukodystrophy, adrenal leukodystrophy</td>
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<tr>
<td>Genetic/metabolic inborn errors of metabolism, amino acidurias</td>
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<tr>
<td>Infectious disorders neuroborreliosis, herpes simplex encephalitis, HIV, neurocysticercosis</td>
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<tr>
<td>Post streptococcal infection, abscess</td>
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<tr>
<td>Vascular disorders CADASIL, Moyamoya disease, carotid dissection</td>
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<tr>
<td>Demyelinating ADEM, ON, TM, NMO</td>
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<tr>
<td>Nutritional B12 or folate deficiency</td>
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<tr>
<td>Neoplastic lymphoma, astrocytoma</td>
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<tr>
<td>MERRF—myoclonic epilepsy with ragged red fibers; MELAS—mitochondrial encephalopathy with lactic acidosis and stroke-like episodes</td>
</tr>
<tr>
<td>LHON—Leber hereditary optic neuropathy; CADASIL—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy</td>
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such as African-American children having a higher incidence, supports a genetic influence. Genome wide association, linkage studies and single-nucleotide polymorphism analysis point to an association of multiple sclerosis in both children and adults with human leukocyte antigens (HLAs) contained within the major histocompatibility complex especially the HLA-DRB1*1501 allele with an odds ratio of 3 (Disanto et al. 2011; Waubant et al. 2016).

The diagnosis of multiple sclerosis is based on the history and neurological examination as well as MRI and the exclusion of alternative diagnoses (Table 12.4, Fig. 12.2). Multiple sclerosis typically produces neurological signs and symptoms that are waxing, waning and linked to changing locations in the brain and spinal cord over time, lesions, which can be well visualised using MRI. The use of the McDonald diagnostic criteria of the International Panel on Diagnosis of multiple sclerosis in adult was recently revised in 2010 and previous versions have resulted in earlier diagnosis of multiple sclerosis with a high degree of specificity and sensitivity; these criteria have led to fewer false positives and allow earlier initiation of therapy (Sadaka et al. 2012). These criteria have been modified for paediatric use by the IPMSSG to provide definitions for paediatric multiple sclerosis, CIS, ADEM and NMO in 2012 (Table 12.3; Krupp et al. 2013; Chitnis and Pohl 2016). A diagnosis for multiple sclerosis can be satisfied by any of the following criteria:

1. Two or more non-encephalopathic (non-ADEM) clinical inflammatory CNS events separated by more than 30 days and involving more than one area of the CNS;
2. One nonencephalopathic event typical of multiple sclerosis with magnetic resonance findings consistent with the 2010 Revised McDonald Criteria for dissemination in space and in which the MRI shows at least one new enhancing or nonenhancing lesion consistent with dissemination in time;
3. One ADEM episode followed by a nonencephalopathic clinical event, 3 or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 McDonald criteria for dissemination in space;
4. A first, single, acute event that does not meet ADEM criteria and whose MRI findings are consistent with the 2010 McDonald criteria for dissemination in space and time, applying only to children >12 years.

These guidelines also provide several radiological criteria that have been tested with respect to their ability to establish a diagnosis of multiple sclerosis in children based on dissemination in time and space. Characteristics of MRI lesions that lead one to a diagnosis of multiple sclerosis are lesions in a periventricular location, hypointense lesions on T1 imaging and the absence of bilateral diffuse lesions. A long-term follow-up study using the IPMSSG criteria in children with CNS demyelination demonstrated the usefulness of these guidelines (Peche et al. 2013; Banwell et al. 2016).

Cerebrospinal Fluid in Multiple Sclerosis

Younger children with multiple sclerosis tend to have higher CSF neutrophil counts than older children or adults while oligoclonal bands as evidence of intrathecal immunoglobulin are less likely to appear in younger patients. The absence of CSF IgM has been associated with an increased relapse rate. Proteomic analysis of CSF has demonstrated increased levels of several axoglal proteins localised to the area where the oligodendroglia meet the axonal membrane. Several studies indicate that oligoclonal bands are present in a high percentage of children and adolescents with relapses of multiple sclerosis (Waldman et al. 2014).

Multiple Sclerosis and Cognitive Development in Children

Cognitive development and mood are often affected in children with multiple sclerosis and impairment has been reported in executive function, processing speed, visuomotor integration and attention in several studies, particularly when multiple sclerosis begins in younger children (Amato et al. 2014, 2016; Hosseini et al. 2014). Several longitudinal studies reported cognitive decline in paediatric patients with multiple sclerosis over several years which may be related to diffusion tensor imaging (DTI) studies which show reduced fractional anisotropy
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in the corpus callosum and related areas of white matter (Till et al. 2011, 2012, 2013; Julian et al. 2013). A correlation between reduced fractional anisotropy in white matter and impaired performance in mathematics and processing speed has been reported in children without other white matter imaging changes (Till 2012). White matter changes have also been reported in magnetisation transfer sequences from children with multiple sclerosis. Supporting children and adolescents with multiple sclerosis often requires a multidisciplinary approach that takes into consideration the perspectives of patients and their parents. Support from social workers, psychologists and psychiatrists is often helpful as families deal with the impact of the diagnosis of multiple sclerosis and the side effects of medications needed to treat it. Appropriate sensitive and focused care should include the perspectives of the patient and parents and should be aimed at enhancing individual and family coping (Krupp et al. 2016).

**CLINICALLY ISOLATED SYNDROMES**

Continued observation of the patient over time usually confirms or rules out the diagnosis of multiple sclerosis but the future is less clear with the appearance of initial demyelinating CIS events such as optic neuritis, internuclear ophthalmoplegia or transverse myelitis episodes seen mostly in adolescents and that carry a high risk of conversion to multiple sclerosis. Neuteboom et al. (2008) retrospectively reviewed 117 children below age 16 who initially presented with a monofocal CIS (referable to a single location such as optic nerve, brainstem, hemisphere, cerebellum or spinal cord) or an initial polyfocal CIS. Over a period of 54 months, 31% of children with an initial monofocal event were diagnosed with multiple sclerosis later based on additional demyelinating episodes dispersed in time and space while those who presented with a polyfocal event were diagnosed with multiple sclerosis 13% of the time.

**Figure 12.2** A 14-year-old girl with a diagnosis of multiple sclerosis. (A and D) Axial T2-weighted and (B) FLAIR images showing multiple ovoid shaped hyperintense lesions in both cerebral hemispheres involving the periventricular deep and subcortical white matter. (E) Axial T1-weighted MR image after the intravenous injection of contrast agent shows enhancement of a left frontal lesion indicating active inflammation (arrows on D and E). (C and F) Parasagittal FLAIR images show the typical radial arrangement of the demyelinating plaques following the course of the intramedullary veins also known as Dawson’s fingers (arrow in C). (Images courtesy of Andrea Porretti, MD Johns Hopkins University School of Medicine, Baltimore, USA.)
An elevated IgG index and presence of oligoclonal CSF bands were more often observed in children who developed multiple sclerosis. MRIs were diagnosed with a predetermined scoring system using criteria based on the revised McDonald criteria or the KIDMUS criteria (Banwell 2008) which were highly specific with the McDonald criteria positive in 60% of children with multiple sclerosis versus 7% in the monophasic patients and the KIDMUS criteria positive in 49% of children with multiple sclerosis versus 4% of those with monophasic events. An ADEM-like presentation or lesions in the basal ganglia were more often observed in children who developed multiple sclerosis than polyfocal events and ADEM. These two studies support the notion that isolated demyelinating events are more likely to predict multiple sclerosis than polyfocal events and ADEM.

### ADEM VERSUS MULTIPLE SCLEROSIS

There is often concern about the likelihood that children with ADEM will acquire multiple sclerosis since both are demyelinating disorders. At times the differential diagnosis between ADEM and multiple sclerosis can be confusing, for reasons including that ADEM may recur with signs continuing to meet criteria for ADEM rather than multiple sclerosis, so called multiphasic ADEM. Dale et al. (2000) reported several important differences between patients with ADEM and multiple sclerosis including a much higher incidence of a predemyelinating illness and encephalopathy as well as a much lower incidence of white matter lesions in ADEM than multiple sclerosis. Bilateral optic neuritis was more common in ADEM than multiple sclerosis but unilateral optic neuritis was seen in multiple sclerosis but not in patients with ADEM. From an MRI standpoint Callen et al. (2008) analysed scans from children with first episodes of ADEM as well as multiple sclerosis and found patients with the latter had more periventricular white matter lesions than those with the former although the total number of white matter lesions in both groups was similar. Patients with multiple sclerosis also had fewer bilateral magnetic resonance lesions and more black holes seen on T1-weighted images. The data from Mikaeloff et al. above also support the the statement that ADEM is usually not a harbinger of multiple sclerosis (Dale and Pillai 2007).

### Therapy for Paediatric Multiple Sclerosis

Multiple sclerosis is characterised by CNS inflammation, formation of plaques, demyelination, axonal injury and axonal loss. The pathogenesis of multiple sclerosis is thought to involve the movement of autoreactive T-cells, monocytes and B-cells from the peripheral circulation through the blood–brain barrier into the brain where they attack oligodendroglia and axons to cause demyelination and gliosis (Ciccarelli et al. 2014; Bar-Or et al. 2016). White cells are initially activated in peripheral lymph nodes by self-antigens presented by antigen-presenting macrophages, B-cells and dendritic cells in association with major histocompatibility class II molecules. T-cells activated outside the CNS are re-activated within the brain by local antigen-presenting cells (microglia, astrocytes and B-lymphocytes). Secreted proinflammatory cytokines such as IL-2 and interferon (IFN)-γ attack myelin, stimulate microglial cells and astrocytes, recruit inflammatory cells and induce antibody production by plasma cells. Helper CD4 T-cells and cytotoxic CD8 T-cells are the major types of cells in multiple sclerosis plaques in the brain, while auto-reactive CD4 helper T-cells secrete pro-inflammatory cytokines. Some evidence suggests that T-cells react more strongly to myelin in children than adults with multiple sclerosis and also express more interleukin 17 compared to adults (Kamm et al. 2014).

Medications used to treat multiple sclerosis are shown in Table 12.5 (Brenton and Banwell 2016). Intravenous methylprednisolone is commonly used to shorten severe episodes, especially those that affect vision. The first-line disease-modifying

### Table 12.5 Medications used to treat multiple sclerosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>Used in high doses for acute episodes and those affecting vision</td>
</tr>
<tr>
<td>Interferon β-1a</td>
<td>First line disease modifying interferon (im, sc)</td>
</tr>
<tr>
<td>Interferon β-1b</td>
<td>First line disease modifying interferon (sc)</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>First line disease modifying, synthetic polypeptide (sc)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylation agent second line for aggressive multiple sclerosis (IV)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Pyrimidine synthase inhibitor (oral)</td>
</tr>
<tr>
<td>Fingolimode</td>
<td>Sphingosine-1-PO4, inhibits T and B cells (oral)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Inhibits immune cells (oral)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Antibody blocks white cell entry into brain (Tysabri®, IV)</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Immunosuppressant with considerable heart toxicity</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Monoclonal antibody against pan-B cell marker CD20</td>
</tr>
</tbody>
</table>

Multivalued indexes: ADEM, multiple sclerosis
drugs for children are the interferons β-1a and β-1b that modify the multiple sclerosis disease process when given chronically (Waubant et al. 2001; Ghezzi et al. 2005, 2016; Banwell et al. 2006). The exact mechanism of action for the interferons is not fully understood, but they may act by decreasing the synthesis of inflammatory cytokines–interferon gamma and tumour necrosis factor alpha. Interferon β-1b may also stabilise the blood–brain barrier damaged in multiple sclerosis by blocking apoptosis of the endothelial cells that make up the blood–brain barrier (Haghooy et al. 2012). In adults large randomised double-blind trials (Jacobs et al. 2000) have shown that treatment with interferon β at the time of the first demyelinating event is beneficial for patients with brain lesions on MRI that indicate a high risk of clinically definite multiple sclerosis. The IPMSSG (Chitnis et al. 2012) reviewed the literature on disease-modifying drugs for multiple sclerosis in children in 2012 and found eight studies in children 11–14 years of age given interferon β-1a once a week intramuscularly in doses escalating from 10mcg to 44mcg weekly. These studies all found that the interferons β-1-a and β-1-b were well tolerated and side effects consisted mostly of flu-like symptoms, mild elevation in liver enzymes and reaction at the injection site, with minor side effects rare.

Glatiramer consists of artificial polypeptides that compete with endogenous myelin proteins for uptake into helper T-cells for antigen presentation (Yeh 20110). Ghezzi et al. (2005) examined the disease modifying effect of interferon β-1a, β-1a (Rebif) and glatiramer acetate in a group of 76 adolescents with a mean age at onset of 12.4 years, finding that the mean annualised relapse rate fell from 2.4 to 0.4 in the interferon β-1-a group, 3.2 to 0.8 in the Rebif-Betaferon group and 2.8 to 0.25 in the glatiramer acetate group. Based on this information the IPMSSG recommended that all paediatric patients with multiple sclerosis should be considered for treatment with either a β interferon or glatiramer acetate as first-line therapy. Current data suggests the IFNs and glatiramer acetate are safe and effective therapies in paediatric patients with multiple sclerosis and the group also recommended these first-line medications for children presenting with clinically isolated syndromes as described above. The report recommended dosing should be titrated upward to the adult dose of interferons over several weeks as recommended by the medication label and that appropriate blood testing such as liver function tests should be followed.

Options for children with multiple sclerosis who do not respond to first line medications are less clearly documented (Ghezzi 2014; Chitnis et al. 2016). Cyclophosphamide has been used for children with multiple sclerosis who continue to worsen despite first-line therapy and there is considerable experience with this drug in paediatric oncology. Makhani et al. (2009) reported 17 patients who continued to worsen despite first-line therapy and the majority of children responded with a reduction in relapses and stabilisation 1 year later, however, this drug can cause nausea, vomiting and neutropenia. Natalizumab works by binding to integrin molecules on the blood–brain barrier to block entry of peripheral white cells which initiate the multiple sclerosis process in the brain however this drug is a powerful immunosuppressant and may increase susceptibility to progressive multifocal leukoencephalopathy (PML) in some individuals (Tur and Montalban 2014). Natalizumab is only available in the United States and Europe through restricted distribution programmes.

The newer drugs teriflunomide, fingolimod and dimethyl fumarate have not been used as much in children but have complementary mechanisms to the older drugs and might be expected to provide benefit when first-line drugs have failed. These new drugs also have the benefit of being active when taken orally while older drugs have to be given subcutaneously or intramuscularly. Fingolimod, a sphingosine 1-phosphate receptor modulator, is a new disease-modifying therapy approved by the US FDA in 2010 for the first-line treatment of relapsing forms of multiple sclerosis in adults (Kappos et al. 2010). Further studies evaluating the pharmacokinetics, appropriate dosing and comparisons of efficacy among these agents are needed to determine the most appropriate and evidence-based treatment decisions in this population. The B-cell suppressing drug rituximab has also been used in adult demyelinating diseases and a retrospective series of 11 cases of paediatric multiple sclerosis and neuromyelitis optica has been reported by Beres et al. (2014). Eight patients with neuromyelitis optica, two with relapsing-remitting multiple sclerosis and one with secondary-progressing multiple sclerosis, were treated for a median number of three cycles and 82% reportedly experienced a reduction in relapses. There were no serious infections but three patients had infusion reactions managed with a reduction in infusion rate. Clinical trials of new oral compounds such as fingolimod, teriflunomide and others are currently ongoing.

**ANTIBODY-MEDIATED ENCEPHALOPATHY**

This large group of diseases is heterogeneous both in terms of clinical symptoms and the demonstration of the causative link between the detected antibody and the disease.

**NEUROMYELITIS OPTICA**

NMO or Devic disease usually presents with bilateral optic atrophy and a spinal cord lesion that resembles transverse myelitis and is based on the presence of:

1. A spinal cord lesion extending over three or more vertebral segments on MRI;
2. A brain MRI that does not meet the criteria for multiple sclerosis; and

Brain lesions in NMO are commonly seen in the optic chiasm and area postrema of the brainstem: although once
considered a subtype of multiple sclerosis, it is now thought to be a separate diagnostic entity with a distinct pathophysiology and therapeutic approach. The AQP4-IgG antibody directed against aquaporin-4 water channels is highly specific for NMO while titre in plasma correlates with NMO disease activity. AQP4-antibody-positive plasmablasts which make IgG are selectively increased in the blood of patients with NMO when a relapse is occurring. AQP4-positive patients are more often female (10:1), show a relapsing pattern of disease and exhibit other types of auto-immunity including SLE, Sjogren syndrome, autoimmune thyroid disease and myasthenia gravis (Jurynczyk et al. 2014). Successful treatment is associated with a fall in AQP4-IgG and therapies directed at B cells such as rituximab and plasma exchange are more effective than interferon treatments used in multiple sclerosis. AQP4-positive sera from humans has been shown to reproduce the NMO pathology in mouse spinal cord slices when combined with human complement. Glutamate-mediated neurotoxicity has also been implicated in the NMO-IgG mediated neuropathology. NMO spectrum disorders can also be diagnosed in patients affected by AQP4-IgG seronegative but are seropositive for antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG), with these patients generally younger at onset of symptoms (Hardy et al. 2016).

From a clinical standpoint the oligoclonal bands found in approximately 90% of CSF samples from patients with multiple sclerosis are found in only 18% of patients with NMO. Brain lesions in NMO tend to be located in regions where there is high expression of the AQP4 receptors on water channels such as the diencephalon, hypothalamus and aqueduct. MRI in NMO often shows lesions in optic nerves and spinal cord that are hyperintense on T2 weighted images and hypointense on T1-weighted images and which enhance with gadolinium (Hardy et al. 2016). Inflamed lesions enlarge due to oedema in the acute phase and may persist for months during which time they become atrophic (Kister et al. 2013). However, despite their differences from patients with multiple sclerosis affected by NMO, they may also have lesions that do fulfill criteria for multiple sclerosis. The reason for the long segment lesions seen in NMO spinal cord lesions is not understood although studies with optical coherence tomography (OCT) have shown neuroaxonal damage that reflects damage to the retinal ganglion cells in NMO is greater than in multiple sclerosis, which is consistent with the clinical observation of more severe visual dysfunction in NMO than in multiple sclerosis (Bouyon et al. 2013). Infections precede episodes of relapse in NMO about 30% of the time and these patients may be more susceptible to tuberculosis as well as human immunodeficiency virus infections.

For treatment of acute episodes of NMO corticosteroids and plasma exchange are generally the first line of therapy and methylprednisolone at 1000mg/day for 5 days for adults is generally given as in multiple sclerosis. Plasma exchange given every other day for 2 weeks is also reported to be effective by reducing the level of the AQP4 antibody and cyclophosphamide as given for refractory multiple sclerosis in children can also be useful (Wingerchuk et al. 2004; Mealy et al. 2014); azathioprine has also been given to patients with NMO to suppress T cell function. Mycophenolate (mofetil) has also been reported to reduce the relapse rate in NMO and the monoclonal antibody rituximab directed at B cells has been reported to help patients with NMO in small trials while IVIG has also been reported to show activity in NMO by reducing levels of IgGg. On the other hand some therapies used for multiple sclerosis such as interferon-β may make NMO worse by increasing levels of the NMO antibody; this is consistent with evidence that multiple sclerosis and NMO disease activity may involve different groups of T-cells.

**ANTI-MYELIN OLIGODENDROCYTE GLYCOPROTEIN ENCEPHALITIS**

Antibodies to myelin oligodendrocyte glycoprotein (MOG) have been implicated in the pathogenesis of multiple sclerosis and can induce demyelination in animal models of multiple sclerosis (Bansal et al. 2013). MOG also appears to be a major target of the humoral immune response in children with inflammatory demyelinating disorders of the CNS (Thulasirajah et al. 2016). Brilot et al. (2009) investigated the occurrence of antibodies to native MOG in 47 children during their first episode of CNS demyelination related to either ADEM (n=19) or CIS (n=28) and compared them to a comparison group of healthy children using a cell based bioassay. Forty per cent of children with ADEM or CIS had high serum immunoglobulin G (IgG) titers to nMOG while none of the control children had anti-MOG antibodies. In contrast only three children in the demyelinating group had IgM antibodies, all of whom were in the ADEM group. Anti-nMOG IgG titers did not differ between the ADEM and CIS group and did not predict conversion from CIS to multiple sclerosis during a mean 2-year follow-up. IgG antibodies to nMOG not only bound to the extracellular domain of nMOG but also induced natural cell-mediated killing of nMOG-expressing cells in vitro. These auto-antibodies may also have significance as markers for the persistence of demyelination (Brilot et al. 2009).

Lalive et al. (2011) measured serum anti-MOG antibodies using ELISA and flow cytometry in 11 children with ADEM, 22 with multiple sclerosis, seven with viral encephalitis with healthy controls and their Epstein-Barr virus (EBV) serostatus also determined in 13. Anti-MOG antibodies were detected in children with demyelination and these antibodies were highly reactive in the group with ADEM. Anti-myelin basic protein reactivity was detectable equally in all groups but the presence of this or anti-MOG did not associate with EBV serostatus, age, sex, or disease course. Probstel et al. (Probstel et al. 2011) reported a prospective 5-year study of 77 children at the onset of demyelinating diseases, 25 of whom had immunoglobulin antibodies directed at MOG. Anti-MOG antibodies declined rapidly in all 16 patients with monophasic ADEM and one patient with a CIS however in six of eight (75%) children
eventually diagnosed with multiple sclerosis anti-MOG antibodies persisted with a secondary increase in titre over time. These anti-MOG antibodies were predominantly IgG1 and their binding was blocked by anti-MOG antibodies derived from an animal model of autoimmune encephalitis. Highly reactive anti-MOG antibodies declined rapidly in children with viral encephalitis but remained elevated in children with demyelination. This data suggests that the persistence of anti-MOG antibodies may have prognostic value for diagnosing childhood multiple sclerosis versus monophasic ADEM. Patients with NMO who have anti-MOG antibodies as well as antibodies to AQP4 have been reported to have a milder phenotype than patients without anti-MOG antibodies (Sato et al. 2014). Baumann et al. (Baumann et al. 2015) compared the clinical and radiological features of paediatric patients with ADEM and with and without anti-MOG antibodies, finding that the group with anti-MOG antibodies had an MRI characterised by large, bilateral and widespread lesions in the brain, with longitudinally extensive transverse myelitis and a favourable clinical outcome compared to children without MOG antibodies.

ANTI-GLUTAMATE RECEPTOR ENCEPHALOPATHIES AND RELATED DISEASES

The discovery of childhood encephalopathy associated with the presence of anti-NMDA receptor antibodies appears to be the ‘tip of the iceberg’ as many new auto-antibodies to synaptic proteins associated with neurological disorders are continuing to appear in the literature (Vincent et al. 2011; Irani et al. 2014; Leyboldt et al. 2014; Rossi 2014): this large group in which the best described entity is the anti-NMDA encephalopathy is also discussed in Chapter 19. Anti-NMDA receptor encephalopathy presents as a dramatic delirium with agitation and movement disorder that can rapidly deteriorate to coma with respiratory failure and the need for ventilation and management of autonomic instability in an intensive care unit. In the classic form it presents in young women with ovarian cysts or teratomas and removal of the cyst rapidly leads to clearing of the sensorium (Gresa-Arribas et al. 2014). In such individuals the anti-NMDA antibody within the CNS is related to cross reaction with NMDA neuronal receptors within the ovarian teratoma. CSF anti-NMDA antibody titres within the CSF are more closely related to outcome than those in the serum with this disorder relatively specific for neurons. However, Titulaer et al. (2014) recently reported overlapping demyelinating syndromes in patients with anti-NMDA receptor encephalitis. A small number of patients with anti-NMDA receptor encephalitis also have clinical or radiological phenotypes suggestive of multiple sclerosis, ADEM or NMO and are seropositive for MGO-Ig or AQP-IgG (Hardy et al. 2016). Another large emerging group of auto-antibody disorders in children presents as encephalitis with refractory seizures, status epilepticus and antibodies to the inhibitory GABA-A receptor (Petit-Pedrol et al. 2014). Similarly, human disorders have been associated with autoantibodies to the GABA-B receptor (above) as well as to the metabotropic glutamate receptor 5, the AMPA glutamate receptor and glutamic acid decarboxylase (GAD), the synthetic enzyme for GABA (Petit-Pedrol et al. 2014).

STREPTOCOCCAL INFECTION-RELATED DISORDERS

Sydenham chorea, which has mostly disappeared from developed countries, is one of the major manifestations of rheumatic fever but can be observed in isolation. Bilateral or unilateral chorea is associated with head movement and grimacing as well as behaviour alterations, with treatment associated with anti-streptococcus treatment with steroids. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are probably a different entity although the syndrome remains controversial (Marcello and Martino 2013). It is defined by the presence of an obsessive–compulsive disorder and tics with abnormal movements precipitated by streptococcal infections and frequently relapsing (Dale et al. 2002; Mell et al. 2005; Singer et al. 2005; Singer et al. 2015).

HASHIMOTO ENCEPHALOPATHY AND ANTI-THYROPEROXIDASE ANTIBODIES

Hashimoto encephalopathy is characterised by the presence of anti-thyroperoxidase antibodies (anti-TPO) in a child affecting acute encephalitis with predominant seizures, neuropsychiatric symptoms and an alteration of consciousness or dystonia (Castillo et al. 2006); it is also a chronic disease that relapses in many individuals. The role of anti-TPO antibodies in the causation of the neurological symptoms is not confirmed and they might be only a marker of the disease. In a recent review we studied eight individuals with Hashimoto encephalopathy with compatible clinical symptoms and a median anti-TPO titer of 2838.5IU/ml, (range 812–8550IU/ml) (Mamoudjy et al. 2013). For these individuals and those mentioned in previous publications median age at onset was 12 years (range: 9–15) but an affected child aged 2 years and 10 months has also been reported (Erol et al. 2011). Most of the patients were girls with normal thyroid function who had an acute onset while the CSF was frequently abnormal with pleocytosis (13%), high protein titers (63%) and oligoclonal bands (43%). The EEG at onset was abnormal in some individuals but no specific pattern has been described. Similarly, brain MRI was abnormal in 50% of the children in our series with abnormalities involving the white and grey matter usually distinctive enough for clear differential diagnosis from multiple sclerosis (Fig. 12.3). As a result we routinely test for anti-TPO antibody in children with acute encephalitis without clear-cut features of ADEM or those presenting in relapse, unless the clinical and radiological symptoms are...
typical of multiple sclerosis. Hashimoto encephalopathy usually responds to steroid treatment but relapses are frequent: immunosuppressive treatments (cyclophosphamide, mycophenolate-mofetil or azathioprine) have been used but there is currently no consensus concerning their efficacy in the absence of formal results of clinical trials.

**INFLAMMATORY DISEASES OF THE WHITE MATTER THAT MIMIC MULTIPLE SCLEROSIS AND RELATED DISORDERS**

The differential diagnosis of an acute inflammatory disease of the white matter in a given child requires great care because the choice of treatment differs considerably between the various diseases (Hintzen et al. 2016). Many entities cause monophasic or relapsing white matter inflammatory syndromes and some other non-inflammatory entities also induce relapsing white matter disease. All of them should be considered as a possible diagnosis not only at the time of the first acute demyelinating event but even more carefully in individuals with presumed ‘resistant’ multiple sclerosis (Tardieu 2013). These conditions include vasculitis and congenital immuno-genetic diseases as well as tumour, genetic or metabolic diseases and migraine (Table 12.1). Table 12.1 does not aim to provide an exhaustive list of possible conditions but is based on our experience as the national reference centre for neuroinflammatory diseases of the CNS in France. It is the experience of most reference centres that 8–10% of all entities referred receive a different diagnosis requiring a different treatment.

**Clues to the Differential Diagnosis of White Matter Inflammatory Diseases**

The main clinical characteristics will be described for each entity but the following features should challenge the diagnosis of ADEM (or less frequently multiple sclerosis): onset before the age of 1 year; a consanguineous family or the existence of another child in the family that has previously displayed...
severe acute neurological symptoms, a gradual progression of clinical symptoms, any non-neurological symptoms or signs such as liver or spleen enlargement, lymphadenopathy, cutaneous vasculitis symptoms (including livedoid vasculitis) and uveitis. Several atypical inflammatory demyelinating syndromes may present with atypical clinical or MRI findings or poor response to treatments for multiple sclerosis (Hardy et al. 2016). The diagnosis should also be re-evaluated if relapses persist despite treatment in a child previously diagnosed with multiple sclerosis. Similarly, the following neuroradiological symptoms on MRI are infrequent in ADEM and multiple sclerosis: a single lesion, high symmetrical white matter lesions, an absence of lesions of the basal ganglia or brainstem, signs of arachnoiditis or lesions restricted to the brainstem and basal ganglia. A normal MRI despite frank symptoms of encephalitis is frequently observed in very young infants with familial hemophagocytic lymphohistiocytosis while CT can be used to search for calcifications suggesting a more restricted group of diseases including Aicardi-Goutières syndrome and related diseases. Normal CSF results despite an ‘inflammatory appearance’ on MRI or an associated fever are frequent in individuals with hemophagocytic lymphohistiocytosis, whereas high concentrations of protein in the CSF (>1g/l) are more frequently observed in arachnoiditis or tumours than in ADEM. However, none of these clinical or radiological findings is absolute and biological markers are required. In individuals with acute demyelinating inflammatory disease for which a diagnosis of ADEM has not been established determinations should be carried out including complete blood formula, erythrocyte sedimentation rate, C-reactive protein, complement activity, ALT/AST, ferritin, triglycerides, anti-nuclear antibodies as well as sometimes anti-thyroid and anti-neuronal antibodies. Lactate/pyruvate ratios in blood and CSF are useful for the detection of respiratory chain dysfunction, particularly in patients with MRI lesions restricted to the brainstem and basal ganglia.

VASCULITIS

Cerebral vasculitis is one of the most challenging differential diagnoses of multiple sclerosis and ADEM (Table 12.6), defined by neuropathological characteristics while clinical, MRI and biological symptoms are heterogeneous, none being specific. By definition the cerebral vessel walls in cerebral vasculitis are infiltrated by inflammatory cells, usually T lymphocytes which should be distinguished from the more usual perivascular infiltration observed in many inflammatory diseases of the brain where vessels are surrounded by monocytes, B and T lymphocytes. The infiltration of brain vessel walls by lymphocytes during vasculitis induces reactive changes in endothelial cells resulting in ischaemic lesions probably related to local thrombosis (Calabrese 1988). This can occur in vessels of different size (large, medium or small). The types of lymphocytes or monocytes infiltrating the vessel walls are poorly described and little is known of their antigenic specificities in relation to the targeted vessel. It is interesting to speculate on the pathway followed by wall-infiltrating T lymphocytes with the best hypothesis their crossing of the blood–brain barrier at the venule level and re-entering the vessel wall at a different point, maybe after transport through the Virchow-Robin spaces (Bechmann 2007).

Cerebral vasculitides are commonly split into (1) primary CNS vasculitis where cerebral vasculitis occurs in isolation and (2) secondary cerebral vasculitides that occur as part of a systemic multi-organ disease or are associated with a specific biological marker.

**Table 12.6 Different types of inflammatory lesions of cerebral vessels**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary central nervous system vasculitis</strong></td>
<td>Small vessel primary cerebral vasculitis (isolated angitis of the CNS)</td>
</tr>
<tr>
<td><strong>Secondary cerebral vasculitis</strong></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Wegener disease and ANCA-related diseases</td>
</tr>
<tr>
<td></td>
<td>Other pathological conditions with vascular lesions</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasmic antibodies.
of symptoms is specific of a given entity although seizures and chorea are more frequent in SLE and stroke (especially in brainstem or due to sinus thrombosis) in Behcet disease and antiphospholipid syndromes. Diagnostic clues in clinical diagnosis investigations are often found outside of the CNS with special attention to the skin and to the kidney.

Similarly, cerebral vasculitis can induce highly variable modifications of cerebral MRI appearances. Multifocal areas of increased signal in grey and white matter on T2-weighted images, frequently with gadolinium enhancement, are the most typical aspect. These initial lesions result, on repeated MRI, in areas of cortical atrophy. Highly suggestive of vasculitis is the association, on the same cerebral MRI, of acute, gadolinium-enhancing lesions with atrophic areas suggestive of previous acute events. Leptomeningeal gadolinium enhancements are frequent as are more diffuse non-specific hyperintense lesions of the white matter with the same MRI aspects observable in brain lymphoma or in any inflammatory disease of the white matter. Larger cerebral infarcts are also observed which result from large or medium sized arterial obstructions (as observed in SLE, Behcet disease or antiphospholipid syndrome) or cerebral venous thrombosis (more frequent in Behcet disease). Infamed vessel walls can occasionally be highlighted by enhancement after gadolinium injection. Catheter cerebral angiography may also demonstrate medium vessel obstruction although this is a relatively infrequent finding and the procedure is usually to be avoided. Finally, it should be remembered that MRI can be normal despite neuropathological demonstration of vasculitis.

CSF characteristics are very similar in the different brain vasculitides with an elevation of the CSF protein content and pleocytosis. The results of other biological tests to be performed are described in the individual syndromes.

Characteristics of the Different Brain Vasculitides

While the strict definition requires tissue examination infrequently obtained such overlapping symptoms led to various classifications based on the initial symptoms, presumed size of the involved vessels as well as presence or absence of extraneurological symptoms and abnormal biological results. The diagnosis of a primary CNS vasculitis is one of exclusion, keeping in mind that a multi-organ disease can have onset in isolation in the brain to be expressed in other organs after a delay.

Main Syndromes with Secondary Cerebral Vasculitis

Table 12.6 gives a list of diseases in which a cerebral vasculitis can be observed. Only the two most frequent ones will be described here.

Systemic Lupus Erythematosus

Several large series of children with childhood-onset SLE contributed to a better description of the natural history (Bader-Meunier 2005; Benseler 2007; Hiraki 2008; Ramirez-Gomez 2008; Descloux 2009; Levy 2009; Singh 2009). The disease occurs usually in adolescents but 15% of children had symptoms before the age of 8 in one series (Bader-Meunier 2005; Descloux 2009). The most frequent general symptoms at onset are malar rash, arthritis and fever, associated with neurological symptoms in 18–27% of patients in the different series. Neurological symptoms consist of headache (60–66% of patients in the different series), mood disorders (Yu 2007; Muscal 2010) and cognitive dysfunction (29–36%), seizures (20%) and stroke (11–24%) while chorea and abnormal movements are less frequent (4%). Neurological manifestations increase in frequency during the course of the disease (35–60% of patients), usually during acute exacerbations of the disease to subside with improvement of systemic manifestations. Their diagnosis is always a challenge to distinguish between the consequence of an acute cerebral vasculitis, of an adverse effect of treatment or of lesions in other organs leading, for example, to a concomitant high blood pressure.

Cerebral MRI at onset has the same non-specific characteristics as other cerebral vasculitides. Similarly, CSF studies, although usually showing cellularity and high protein content, do not give specific clues. The diagnosis is established considering the multi-site involvement and characteristic biological markers: hemolytic anemia, thrombocytopenia, leuko- and lymphopenia, high antiphospholipid and cardiolipin antibody titres, low CH50 and C4 determinations, high titres of specific auto-antibodies comprising antinuclear antibodies, anti-double-stranded DNA, anti-SSA, anti-SSB, antiSm and anti-RNP antibodies.

Treatment is based on immunosuppressive therapy with high-dose pulses of methylprednisolone, frequently associated with other immunosuppressive agents, the most frequently used being cyclophosphamide and azathioprine.

Behcet Disease

Behcet disease is a systemic disorder that can involve any organ, with neurological symptoms being reported in 20% of individuals (Amman et al. 1985; International Study Group for Behcet’s Disease 1990; Bahabri 1996; Kone-Paut 1997; Kone-Paut 1998; Vaiopoulos 1999; Kari 2001; Al-Araji 2009; Metreau-Vastel 2010; Kone-Paut 2011; Uluduz 2011). (Fig. 12.3) The disease is usually observed in adolescents but also 8–16% of patients who are less than 8 years old. Patients originate more frequently from Mediterranean countries and two-thirds display HLA-B51 (Ohno 1982). Finally, familial cases are observed in 23% of the series from Turkey but 8% of patients from France (Metreau-Vastel 2010; Uluduz 2011). The most frequent neurological manifestations are linked to a high intracranial pressure due to cerebral venous sinus thrombosis (Alper 2001). It can come in isolation while more characteristic Behcet symptoms will be observed during the subsequent course of the disease. The diagnosis should be considered in any child with cerebral venous sinus thrombosis with no obvious cause while a smaller percentage of children have
other neurological symptoms at onset such as focal neurological deficits (Atkinson 2008; Metreau-Vastel 2010) and meningoencephalitis while GBS and isolated transverse myelitis have been observed. The course of the disease is relapsing, sometimes despite treatment. Cerebral MRI can demonstrate venous sinus thrombosis best observed after gadolinium enhancement (Saltik 2004; Metreau-Vastel 2010; Uluduz 2011). In the Turkish series isolated superior sagittal sinus thrombosis was observed in 42% of patients and concomitantly with transverse sinus thrombosis in another 30%, the remaining patients having isolated unilateral transverse sinus or internal jugular vein thrombosis (Ulduz 2011). Other patients have signs of stroke on cerebral MRI. CSF studies are normal in half the patients with erythrocyte sediment rate and C-reactive protein level frequently elevated during active phases of the disease (Metreau-Vastel, 2010). Treatment is with steroids and immunosuppressants, as well as azathioprine and colchicine on a frequent basis. The use of anticoagulation in individuals with cerebral venous sinus thrombosis is not consensual but was undertaken in most of our patients.

Primary Central Nervous System Vasculitis

The diagnosis of childhood primary angiitis of the CNS is based on three criteria: (1) an acquired neurological deficit, (2) angiographic or histological evidence of cerebral vasculitis, and (3) absence of evidence of systemic vasculitides or any other condition to which the findings could be secondary (Calabrese 1992; Salvarini 2007; Elbers 2010). There is a loose and partly negative definition that leads to a further distinction between small vessel primary CNS vasculitis and medium-large primary CNS vasculitis.

Small vessel primary cerebral vasculitis is a rare condition and a very difficult diagnosis. It can affect children at any age with the most common clinical presentations being, in the largest series, seizures (85%), headache (62%) and cognitive decline (54%) (Lanthier 2001; Benseler 2005; Elbers 2010). Interestingly, two patients presented with optic neuritis and two had spinal cord involvement, increasing the risk of misdiagnosis with multiple sclerosis. CSF was abnormal in all patients with increased opening pressure, pleocytosis and elevated protein content. Inflammatory markers in blood are usually elevated, a difference with multiple sclerosis. MRI showed the same various aspects as other CNS vasculitides although lesionals and leptomeningeal gadolinium enhancements were more frequent, with the magnetic resonance angiography normal in all individuals. A definitive diagnosis requires brain biopsy but a difficult task is to determine the site of specimen sampling; to observe a mere perivascular infiltration is not unusual and fails to confirm the expected diagnosis. Lack of specific histological features correlates with inadequate specimen sampling, prolonged time to biopsy and prior steroid treatment (Hutchinson 2010). Treatment consists in high-dose pulses of methylprednisolone associated usually with pulses of intravenous cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate mofetil.

Medium and large vessel vasculitides are more frequent than small vessel vasculitis but there is a large overlap between this entity and ‘transient cerebral arteriopathy’, the most frequent cause of strokes in children, described in Chapter 15 (Chabrier 2000; Sebire 2006; Braun 2009). The usual clinical expression is a stroke or, and less frequently, transient ischaemic episodes. The pathological aspects of vessels are best demonstrated by magnetic resonance angiography, at the level of the A1 segment of the left anterior cerebral artery and M1 segment of the left middle cerebral artery. Several studies have now established that varicella zoster virus (VZV) infection is more frequent in the months preceding the stroke in affected children than in the general population (Sebire 1999; Gershon 2014; Thomas 2014); however, a second and less frequent form of post VZV arteriopathy involves smaller vessels and consists in multiple small infarcts observed within days after acute varicella (Gilden 2009). Finally, bacterial infection or Lyme disease can also induce vasculopathy and stroke with MRI demonstrating vessel wall thickening and gadolinium wall enhancement (Lebas, 2010).

IMMUNOGENETIC DISEASES MIMICKING MULTIPLE SCLEROSIS AND RELATED DISORDERS

Congenital immunogenetic diseases are rare but many of these diseases may involve the CNS. The neurological symptoms are generally not isolated and diagnosis is based principally on extraneurological symptoms, however, this is not always applicable to hemophagocytic lymphohistiocytosis (HLH) (Haddad 1997; Fleddman 2005; Horne 2008) which has several different forms including familial hemophagocytic lymphohistiocytosis (FHLH), Chediak-Higashi disease, Griscelli disease and Purtillo disease (Jenka 2012). HLH is the most frequent form of HLH and results from genetic defects impairing the cytotoxicity of CD8 T lymphocytes. These genetic defects may remain asymptomatic until a trigger, most often a viral infection, induces the uncontrolled polyclonal activation of CD8+ T lymphocytes and macrophages, resulting in the overproduction of cytokines. We recently evaluated children at the onset of the different types of HLH and compared them with children of a similar age diagnosed with ADEM (Deiva, 2012). In HLH, the median age at onset was 2.5 months but the range was wide (0–190 months). Initial symptoms at presentation were not restricted to the CNS in most patients, with fever (>38.5°C) reported in 83% of patients, hepatomegaly in 72%, splenomegaly in 63% and lymphadenopathy in 57%. Neurological symptoms consisted of seizures, impaired consciousness, meningismus and focal motor deficits while common biological signs included pancytopenia, low fibrinogen levels, high liver enzyme levels, hyperferritinemia, hypertriglycerideridemia (all present in more than 90% of patients) and hyponatremia (63% of patients) (Ouaché-Chardin 2006;
Signs of hemophagocytosis were detected on both blood and bone-marrow smears for 66% of patients. However, neurological symptoms were isolated in 7% of the patients in the series of Mahlaoui (2007) and Deiva (2012). Important clues that can direct the physician to the correct diagnosis include young age and consanguinity or the early death of a sibling. Moreover, in this probably inflammatory and acute encephalitis CSF results were normal in 50% of patients, whereas a high protein titer (>0.5g/L) was found in 50% of patients, high cellularity (>10/ml) in 37% and features of hemophagocytosis in 24% (Mahlaoui 2007); similarly, brain MRI at onset was normal in 67% of patients (Fig. 12.4). In patients with abnormal MRI results white matter lesions were more frequently symmetrical and periventricular with signal hypointensity on T1 sequences in HLH than in ADEM whereas lesions of the thalamus, basal ganglia and brainstem were more frequent in ADEM than in HLH. Gadolinium enhancement was slightly more frequent in HLH than in ADEM (33% vs 16%) in our series but this difference was not statistically significant (Deiva 2012). Early diagnosis can be established by carrying out specific immunological tests (including analyses of perforin expression in lymphocytes and of the cytotoxic ability of the patient’s CD8 lymphocytes) before identification of the causal mutation, essential as treatment requires immunosuppression followed by a bone-marrow transplantation (Ouaché-Chardin Paediatrics 2006; Mahlaoui Paediatrics 2007). Other treatments invariably lead to relapses resulting in severe necrosis of the brain parenchyma.

Figure 12.4 (A) Familial lymphohistiocytosis with symmetrical lesions in basal ganglia and white matter lesions in a 2-year-old boy. (B) Lymphoma: two lesions of different ages in an 8-year-old boy. (C, D) axial and (E) coronal images showing: Langerhans cell histiocytosis in a 6-year-old girl with neurodegeneration with bilateral hyperintense lesions of the dentate nuclei, cerebellar white matter, brainstem and parietao-occipital white matter. (Images courtesy of Andrea Porretti, MD Johns Hopkins University School of Medicine, Baltimore, USA.)
TUMOURS MIMICKING MULTIPLE SCLEROSIS

The course of multiple sclerosis, with periods of relapse and remission, observed in more than 95% of children with multiple sclerosis should prevent this condition being confused with tumours, but there are exceptions.

**Oligodendroglioma and low-grade astrocytoma** might initially yield MRI results reminiscent of white matter inflammatory diseases. It may initially lead to the incorrect diagnosis of multiple sclerosis if there are few clinical symptoms. The principal clues are a gradual progression of clinical symptoms or a persistent deficit, the absence of spatial dissemination on initial MRI and of modifications (or only a slight extension) on subsequent MRI scans. Spectroscopy of the pathological lesion may be useful and diagnosis can usually be established on the basis of a biopsy (Vicente 2013; Orphanadou-Vlachou 2013).

**Primary cerebral lymphoma** can be a much more challenging diagnosis. In a review of 29 children with primary CNS lymphoma disease was confined to the brain (n = 26) or meninges (n = 3) with no evidence of systemic lymphoma at presentation (Abla 2011). The median age at diagnosis was 14 years, the youngest patient being 2 years old. The most frequent initial symptoms were headache and nausea (suggesting an increase in intracranial pressure), cerebellar symptoms, seizure and hemiparesis. On MRI 38% of lesions were disseminated in space, with 41% of the lesions found in the basal ganglia and brainstem (Fig. 12.4). CSF analysis was not informative in most patients (only eight of the 26 had positive CSF cytological results for lymphoma) while all had primary CNS non-Hodgkin’s lymphoma (69% had diffuse large B-cell lymphoma, 17% had anaplastic large T-cell lymphoma, 7% had lymphoblastic lymphoma and 7% had Burkitt-like lymphoma) (Abla 2011). To further illustrate diagnostic difficulties an initial brain biopsy of a large white matter lesion in one of our patients indicated only ‘nonspecific inflammatory lesions’. The appropriate diagnosis was finally established when skin lesions appeared four months after the initial neurological symptoms, leading after pathological evaluation of the skin lesion biopsy specimen to the diagnosis of anaplastic large-cell ALK1+ CD30+ lymphoma with detection of the NPM-ALK transcript. This transcript was retrospectively detected in the brain biopsy specimen leading to the establishment of a diagnosis of primary CNS lymphoma.

**Langerhans cell histiocytosis** (LCH) is characterised by the proliferation of dendritic cells associated with chronic inflammation. It is a rare disease observed mainly in teenagers although it may occur at any age. Bone is the most frequently affected tissue (79% of the 603 patients in the Korean registry), followed by the skin (19.2%) but 30% of patients had a multisystem disease (Kim 2014). The frequency of neurological symptoms is not fully established, especially as a primary symptom; however, the most frequent clinical presentation is related to infiltration of the hypothalamic-pituitary region inducing a diabetes insipidus and less frequently growth hormone deficiency or other anterior pituitary hormone loss.

The second presentation is related to mass lesion, either solitary or multifocal, either in meninges or in parenchyma including brainstem (Savardekar 2013). Symptoms are those of increased intra-cranial pressure occasionally with seizures. Among the 1411 patients from the French LCH registry, 57 were identified with one or several mass lesions and on the 20 reported in detail (for therapeutic proposals) 13 were children (1–15 years), ten having diabetes insipidus and hypothalamic-pituitary region involvement as well as three having respectively cerebellar ataxia (as an isolated initial symptom), headache (initial symptom) or a visual field defect (during a late reactivation) (Tin et al. 2011).

The third presentation is the most difficult to diagnose associating behavioural disturbances, learning difficulties, ataxia, dystarthisia and motor spasticity (Mimouni 2010; Ehrardt 2013). A progressive decline can be observed leading to the designation of Langerhans cell histiocytosis-associated neurodegeneration. It is the rarest initial presentation but was observed during the course of disease in 153 out of 308 LCH patients with MRI findings in the histiocytic society registry and seven out of 29 similar patients in a series from Sweden (Grois 2010; Laurencikas 2011). MRI findings in these patients include symmetrical hyperintense signal in T1-weighted images in the cerebellar grey and white matter, cerebellar atrophy, T2-weighted hyperintense changes in the pons and T1-weighted hyperintensity of the globus pallidus (Fig. 12.4). No systematic study of the CSF in LCH has been published. Treatment (apart from correcting dysfunctions such as diabetes insipidus) depends on localisation and stage of disease and uses mostly chemotherapy, vinblastine being presently the standard treatment (Tin et al. 2011).

OTHER GENETIC DISEASES MIMICKING INFLAMMATORY WHITE MATTER DISEASES

**Leukoencephalopathies linked to mutations indirectly modifying intra-cerebral inflammation status.** This is a large group of rare diseases progressively being discovered. Their clinical symptoms are usually sufficiently different from ADEM and multiple sclerosis to avoid confusion but borderline cases can be observed. The best example is **Aicardi-Goutières syndrome**, with this neonatal-onset encephalopathy associated with microcephaly, brain calcifications and high interferon-alpha concentration in the CSF (Rice 2007); however, MRI demonstrates the presence of large white matter lesions and clinical onset may occur later in childhood. This syndrome is linked to various mutations affecting RNA metabolism or to proteins that normally prevent the self-activation of innate immunity by cell-intrinsic components (Crow 2007; Rice 2009). Another example is provided by a mutation of the colony-stimulating factor 1 receptor gene which has recently...
been demonstrated to be the cause of a dominant form of leukoencephalopathy probably resulting from microglial dysfunction (Rademakers 2012).

Mitochondrial respiratory chain deficits are the metabolic diseases most frequently misdiagnosed as optic neuritis, brain-stem encephalitis or multiple sclerosis. These deficits can present with optic neuropathy, the most common form of which being Leber hereditary optic neuropathy (Harding 1992). The mutations characteristic of this disease should be sought in individuals with relapsing optic neuritis or non-resolving optic neuritis. Similarly, acute brainstem encephalitis may have clinical and radiological symptoms very similar to those of mitochondrial diseases, including Leigh disease in particular. An evaluation of lactate content and of lactate/pyruvate ratio in blood and CSF and spectroscopy focusing on the white matter lesions as well as a direct study of respiratory chain activity in lymphocytes, fibroblasts or muscle biopsy specimens should lead to establishment of the correct diagnosis.

The detection of non-specific incidental white matter changes in children with headache, or more specifically migraine, is now well established (Candee 2013). Three recent large series demonstrate in respectively 941, 1008 and 449 children with headache a similar rate of 4.3–6% of white-matter hyperintensities with a non-significant trend for a higher prevalence in migraine with aura than without aura (Bayran 2013; Mar 2013; Yilmaz 2013). Lesions are only supratentorial and non-progressive, more frequently in the deep white matter than periventricular with a mean size of 5.1 (SD 4.5mm) in one of the studies (Fig. 12.5). The distinction from multiple sclerosis is usually easy on clinical grounds as well as differences in signal intensity, localisation and absence of gadolinium enhancement.

Figure 12.5 Migraine. Small foci of hyperintense signals within the supratentorial white matter on T2-weighted and FLAIR signals in two adolescents (upper and lower panels respectively). (Courtesy of Andrea Porretti, MD Johns Hopkins University School of Medicine, Baltimore, USA.)
Multisystemic granulomatous disorders are rare in children and isolated CNS forms are even more so. It is a large group of diseases that include sarcoidosis, polyarteritis nodosa, Wegener disease, and anti-neutrophil cytoplasm antibody (ANCA)-related diseases (Rottem 1993; Bosch 2006; Demirkaya 2012), Whipple disease (Louis 1996; Scheld 2003) as well as infections (cat scratch disease). Only the first two of these disorders will be reported here considering their rarity.

**Sarcoidosis**

Sarcoidosis is predominantly a lung disease with neurological symptoms in 5–15% of young adults consisting of aseptic meningitis, hypothalamic and pituitary dysfunction, peripheral and cranial neuropathy as well as less frequently CNS space-occupying lesions. Only small series of children with neurosarcoidosis have been reported but some of the described patients did have an isolated neurosarcoidosis (Kone-Paut 1999; Anand 2013). A large survey in France of 205 paediatric patients with interstitial lung diseases indicated that 21 were related to a sarcoidosis. Among these 21 children, three had a disease restricted to the lung and 18 were multisystemic with six having symptoms of uveitis and only one a neurological involvement (Nathan 2012). In another publication 29 children with neurosarcoidosis were gathered, four of them having an isolated neurosarcoaidosis and two others having neurological symptoms plus uveitis only (Bauman 2003). The key symptoms for the whole group were uveitis (9/29), seizure (11/29), cranial nerve involvement (6/29), intra-cranial hypertension associated with hypothalamic dysfunctions (6/29), enlarged lymph nodes, liver and spleen, arthritis and swelling of the parotid gland. A recent review added three other individuals of isolated neurosarcoidosis in children (Anand 2013).

In CSF elevated opening pressure, lymphocytosis and elevated protein content are common but none of the published series clarified the percentage of children with normal CSF. Brain MRI can demonstrate granulomata in the parenchyma which frequently are enhanced after gadolinium injection, with diffuse gadolinium enhancement of basal meninges and periventricular white matter lesions (Fig. 12.6). Elevation of serum angiotensin-converting enzyme helps in the diagnostic process if present but elevation is not constant, with the same being true for hypercalcemia. A biopsy of the lesion can be required to establish the diagnosis and show non-caseating granuloma with multinucleated giant cells. Treatment uses steroids usually as high dose methylprednisolone pulses associated with immunosuppressive drugs but no formal study has been published.

**Polyarteritis Nodosa**

Polyarteritis nodosa (periarteritis nodosa, PAN) is a rare vasculitis of the medium and small-sized arteries that can induce
neurological involvement with the medium age at onset between 7.9 and 8.6 years in three recent series of patients (Eleftheriou 2013; Falcini 2014; Mondal 2014). The presenting symptoms were fever, myalgia and skin involvement in almost all patients and, in a smaller proportion, hypertension or renal involvement as well as neurological signs. Diagnosis is usually established by skin biopsy showing necrotising vasculitis of the medium sized vessels. It is highly unusual but sometimes necessary to perform a nerve or muscle biopsy to establish a diagnosis of PAN in a patient with isolated severe multiple mononeuropathy. CNS manifestations are less frequent and result from vascular obliteration and aneurysm formation resulting in stroke or hemorrhage. Cyclophosphamide and steroids are the most frequent initial treatment: in the published series only 52% of patients were off therapy after a mean follow-up of 6 years and relapse rates were 35% and 33% (Eleftheriou 2013; Falcini 2014).

### AUTO-INFLAMMATORY DISORDERS WITH NEUROLOGICAL INVOLVEMENT

**Neonatal onset multisystem inflammatory disease (NOMID) or Chronic inflammatory neurological cutaneous articular syndrome (CINCA)**

*CINCA* (aka NOMID and related diseases). Auto-inflammatory syndromes are monogenic diseases caused by mutations of genes coding for proteins involved in the regulation of the inflammatory response. A subgroup called ‘cryopyrin-associated periodic syndromes’ (CAPS) is caused by mutations in the *NLRP3* (or *CIAS1*) gene encoding for cryopyrin, a protein that activates IL-1beta (Caso 2013). This includes chronic infantile neurological cutaneous and articular syndrome (CINCA), Muckle–Wells syndrome and familial cold urticaria in order of decreasing severity. CINCA syndrome appears during the first year of life, associating fever, urticaria-like skin rash, uveitis, headache, arthralgia and fatigue. Later on, episodes of severe headache due to increases intra-cranial pressure and chronic polymorphonuclear aseptic meningitis are variably associated with uveitis, papilledema, optic nerve atrophy with decreased vision and perceptive deafness. MRI is not specific, showing in individuals with severe ventriculomegaly and signs of arachnoiditis. Treatment uses different types of anti IL-1 agents such as anakinra, a recombinant, non-glycosylated version of human IL-1 receptor antagonist that are effective also on neurological symptoms (Neven 2010).

**SUSAC syndrome**

SUSAC syndrome is a rare disorder. A recent review gathered 304 affected individuals in the literature, children representing less than 10% with the youngest reported patient being 8 years old (Dörer 2013). It is viewed as an autoimmune disease leading to occlusion of microvessels and characterised by recurrent episodes with visual disturbances due to lesions on the retina, hearing deficit and neurological symptoms. The latter are very similar to those observed during vasculitis with headache in 80% of the 304 published cases, frequently associated with cognitive impairment; however, the characteristic triad is usually not fully present at onset. CSF is abnormal with elevated protein content (the presence of oligoclonal bands is unusual but described) and mild lymphocytic pleocytosis with diagnosis established on the demonstration of retinal artery occlusion by fluorescein angiography, of hearing deficit and usually non-specific but sometimes highly characteristic MRI brain lesions. The most frequent consists of numerous strongly hypointense signals in the corpus callosum and less frequently in the periventricular area on the T1-weighted images; however, hypo-intense lesions can be observed in any location both supra- and infra-tentorial. Significantly they have not been described in the spinal cord. The best treatment is not established but requires steroids and immunosuppressive agents.

### CEREBELLITIS

**ACUTE CEREBELLAR ATAXIA AND ACUTE CEREBELLITIS**

Acute ataxia may be the consequence of an inflammatory reaction within the cerebellum and is sometimes differentiated from acute cerebellitis, the latter being more severe (Gill 2010). Here the two terms are considered as equivalent with benign and severe forms, acute cerebellar ataxia being a clinical description and acute cerebellitis referring to the pathophysiology.

Acute cerebellar ataxia is characterised by a sudden onset of ataxia following, or in association with, a viral illness. Frequency and usual benign outcome precluded the constitution of large prospective population-based cohorts with most of the reported series hospital-based and probably skewed toward those affected more severely. Acute cerebellar ataxia can be observed in children of all ages although in a combined series of 112 individuals half were affected before 4 years of age (Connolly 1994). The onset of ataxia is usually acute with a marked gait ataxia and dysmetria, the child adopting a widely based stance or possibly avoiding standing altogether. Even in the sitting position a young child may look unsteady. Hypotonia, tremor of the extremities, head and trunk, are usually obvious and in older children speech is slow without the usual intonations with syllables uttered in an explosive manner.

At the onset of the disease clinical evaluation should carefully explore associated symptoms and signs relating to three areas. The first is related to eye movement: nystagmus is frequently observed (although no precise frequency can be established due to large variations between series) whereas sudden random movements of eyes either spontaneously or during voluntary movement are less frequent [but raise other possible diagnoses,
including opsoclonus-myoclonus syndrome (OMS). The second findings are those which suggest either meningitis or raised intracranial pressure (headache, depressed level of consciousness and vomiting while neck stiffness is unusual): any symptom suggesting raised intracranial pressure should prompt further steps detailed below. Finally, myoclonic movements of the arms and any brainstem-related symptoms may be present and tend to be associated with a more severe phenotype.

The respective frequencies of different viral infections that frequently precede onset of neurological symptoms vary according to country and vaccination recommendations. Clinical experience and a few systematic studies suggest that varicella, mumps and EBV infections are more frequently associated with acute benign cerebellitis than other common viral infections (Connolly 1994; Amlie-Lefond 2009). The CSF is abnormal in about half of the patients with a mild pleocytosis, mostly lymphocytic and moderately elevated protein content. In most individuals affected by benign acute ataxia the brain MRI is normal.

The disease is self-limited in benign acute inflammatory ataxia by definition. The ataxia resolves completely with an average duration of cerebellar signs of 2 months although mildly affected children can recover completely within a week. Individuals affected benignly do not require any treatment but if more affected or very uncomfortable children a good symptomatic response has been seen with the use of a short course of steroids (usually 1mg/kg of prednisone for 7 days although no formal study has been conducted).

Acute cerebellitis can induce very severe symptoms related to an intense inflammatory reaction with leukocyte infiltration of brain parenchyma and the opening of the blood-brain barrier to soluble factors and water. This leads to posterior fossa or brainstem swelling and should be regarded as a medical and sometimes neurosurgical emergency (Roulet Perez et al. 1993; Kamate et al. 2009). Neurological symptoms usually suggest raised posterior fossa pressure: these include nausea, repetitive yawns, vomiting as well as sixth nerve palsy (due to compression at the brainstem), reduced consciousness level and frequently papilloedema. Symptoms more directly related to brainstem involvement are altered respiratory pattern, blood pressure changes or other cranial nerve palsy and may reflect a life-threatening situation associated with herniation either upward through the tentorium or downward through the foramen magnum (Shkalim 2009). If it is not an immediate life-threatening situation MRI should be performed. Various aspects of early brain imaging in acute and severe cerebellar ataxia have been described (Shoji 1991; Horowitz 1991, 1995; Sawaishi 1999; Soussan 2003; De Brucker 2004; Matsukuma 2008) the first being a global swelling of the cerebellum and brainstem with a compressed fourth ventricle and occasionally signs of herniation either upward transtentorially or of the cerebellar tonsils into the foramen magnum. In individuals affected less acutely two other abnormalities are observed, which are usually mutually exclusive: an increased signal on T2 and FLAIR at the level of the cerebellar cortex that can be either uni- or bilateral or increased signal around the dentate nucleus and of the cerebellar white matter. Finally, MRI may demonstrate supratentorial lesions in association with infratentorial ones and therefore suggest a multifocal inflammatory process (usually ADEM; Fig. 12.7).

Acute swelling of the cerebellum is an emergency usually requiring medical intensive care and sometimes neurosurgical measures (de Ribaupierre et al. 2005). High dose pulses of methylprednisolone are probably the best medical treatment which may help to reduce the swelling and obviate the need for surgical intervention. However, surgical decompression of the posterior fossa may be life-saving when there are signs of brainstem compression or tonsillar herniation (Asenbauer et al. 1997; Hamada et al. 2001; Cohen et al. 2014). While complete recovery is observed in the majority, with disappearance of MRI lesions on subsequent imaging, severe cerebellar destruction and atrophy have also been described (Hayakawa 1995; Tabarki 1998; Kamate et al. 2009). If this occurs the clinical consequences are a combination of predominantly cerebellar motor dysfunction with an accompanying cognitive deficit. Very few neuropathological studies are available however and they are restricted to patients who died after very severe inflammation and posterior fossa oedema (Roulet-Perez 1993).

**PERSISTENT, RELAPSING CEREBELLAR ATAXIA**

Persistent cerebellar ataxia incorporates ataxia of both trunk and limbs, dysarthria and a variety of behavioural problems which persist over time. No strict definition has been proposed but if a cut-off for persistent symptoms is set at two months from onset it would represent a third of affected children. Symptoms can be relieved by steroids (usually prednisone 1mg/kg for 10 days and in individuals affected more severely by intravenous high dose methylprednisolone); however, if cerebellar ataxia persists after two to three months the diagnosis should be carefully re-evaluated. Persistence of marked cerebellar ataxia is associated with intellectual disability and behavioural abnormalities more frequent if cerebellar atrophy or patchy necrosis are observed on MRI performed three months after onset (although no optimal date to evaluate prognosis as been defined).

Relapsing acute cerebellar ataxia is unusual and should be differentiated both from the transient exacerbation of a known pre-existing ataxia during an intercurrent febrile episode and also from acute disseminated relapsing inflammatory diseases of the CNS such as vasculitis or multiple sclerosis. A re-evaluation of the diagnosis is also mandatory, especially if the CSF remains persistently normal.

**Differential Diagnosis of Acute Cerebellitis**

Several conditions can mimic acute inflammatory cerebellar ataxia (Table 12.7), being mostly the following:

*Intoxications.* These are usually an easy diagnosis. The spectrum of responsible agents varies between countries and
cultures, most frequently appearing in western countries as alcohol, benzodiazepines, neuroleptic and antiepileptic drugs.

Ischaemic stroke. Ataxia of very sudden onset (or observed at awakening) can be the only or the main symptom of an ischaemic stroke. It is usually associated with some degree of hemiparesis, somnolence or cranial nerve palsy. The MRI will provide the main clue showing on FLAIR and diffusion-weighted sequences a small lesion either in the brainstem (and sometimes lateralised with a sharp demarcation at the mid-line), cerebellum or basal ganglia. A frequent aetiology is an arterial wall dissection at the level of one of the vertebral arteries or less frequently of the basilar artery, producing a thrombus and small down-stream embolus.

Channelopathies and other inherited familial episodic ataxias. These are very rare conditions. The diagnosis depends on the family history as the disease is commonly transmitted as an autosomal dominant trait. There are several types caused by a mis-sense mutation in the potassium channel gene KCNA1 or by mis-sense or nonsense mutation in the calcium-channel gene CACNA1A. In the absence of a family history the diagnosis is more difficult and will be suggested by repetitive bouts of acute ataxia. Ion measurements during symptomatic episodes may give a lead to the relevant genetic test.

Leigh disease and other mitochondrial disorders. Repetitive episodes of ataxia with either brainstem, basal ganglia or cerebellar lesions on MRI should raise the possibility of mitochondrial disorders, especially Leigh disease in a young child. Clues to the diagnosis, apart from the MRI features, are the lactate level in CSF (usually higher than 2mmol/l) and lactate/pyruvate ratio in serum (>20). This syndrome may be the consequence of a variety of causal genetic mutations in both mtDNA and nuclear DNA (see Chapter 9).

Other metabolic diseases. Hyperammonemias, Hartnup and maple syrup urine variants can have acute or relapsing ataxia as an isolated initial symptom although this is unusual.

Cerebellar tumours. An acute onset with ataxia is unusual but possible. Neck stiffness, vomiting and associated neurological signs will prompt an MRI.

Acute labyrinthitis. This is in fact unusual but nausea, vertigo and nystagmus are clues to diagnosis. Benign paroxysmal vertigo in toddlers is characterised by a sudden, unsteady gait in a child who holds on to a parent for stability. The very short duration and sometimes history of migraine in one or both parents will suggest the diagnosis.

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### Table 12.7 Differential diagnosis of acute ataxia

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<tr>
<th>Acute cerebellar ataxia and acute cerebellitis</th>
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<tr>
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<td>Acute Disseminated Encephalomyelitis (ADEM)</td>
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<td>Intoxications</td>
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<td>Stroke</td>
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<td>Leigh diseases and other mitochondrial disorders</td>
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**Persistent and relapsing cerebellar ataxia**

| Acute inflammation of cerebellum               |
| Opsoclonus-myoclonus syndrome                  |
| Channelopathies                                |
| Leigh diseases and other mitochondrial disorders |
| Other metabolic diseases                       |
| Acute labyrinthitis                            |

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**Figure 12.7** Acute cerebellitis: (A) global swelling of the cerebellar cortex with increased signal in T2-weighted image (B) bilateral increased signal around the dentate nucleus.
OPSOCLONUS-MYOCLONUIS SYNDROME AND OTHER PARA-NEOPLASIC DISORDERS

The chapter on paraneoplastic disorders in paediatric neurology used to be very short. Many syndromes are now recognised: some such as anti-NMDAR antibody encephalitis, anti-Hu encephalitis (Honnorat 2013) or Lambert-Eaton syndrome are only rarely associated with a tumour in children whereas others like OMS are associated with a neuroblastoma in the majority of children. Finally, it is now the custom to search carefully for remote lymphomas or tumours in a child with an evolving inflammatory-like encephalopathy. We followed, for example, a 15-year-old girl with a progressive spastic tetraparesis and abnormal signal on T2 weighted MRI in cortico-spinal pathways that led to the discovery of an intra-abdominal lymphoma.

Two of the well characterised paraneoplastic syndromes are described here.

OPSOCLONUS-MYOCLONUIS SYNDROME
(Dancing Eye syndrome, Kinsbourne’s syndrome)

OMS is now defined by the association of three of the following four diagnostic criteria: (1) opsoclonus; (2) ataxia/myoclonus; (3) behavioural change and/or sleep disturbance; (4) neuroblastoma. Opsoclonus refers to rapid, conjugate, multidirectional eye movements more frequently intermittent than permanent. Ataxia has no special features and, at onset, a false diagnosis of acute inflammatory cerebellar ataxia is frequent. Myoclonus usually involves the arms and varies from tremulous myoclonia to multifocal jerks, whereas others like OMS are associated with a neuroblastoma in the majority of children. Finally, it is now the custom to search carefully for remote lymphomas or tumours in a child with an evolving inflammatory-like encephalopathy. We followed, for example, a 15-year-old girl with a progressive spastic tetraparesis and abnormal signal on T2 weighted MRI in cortico-spinal pathways that led to the discovery of an intra-abdominal lymphoma.

The natural history of OMS has been better defined through a genetic predisposition to auto-immunity), the detection of auto-antibodies against Purkinje cells (although none has been fully characterised) and the good effect in some patients of treatment directed against antibody-producing lymphocytes. It is likely that a cellular auto-immune response is also present in all or in subgroups of patients.

In the long term the main outcome risk is the occurrence of significant or severe cognitive and neuropsychological deficits while motor outcome is normal or near normal. Within the UK series 7% of patients had a monophasic and sometimes benign disease whereas 61% had a chronic relapsing disease and 32% had several acute exacerbations but were symptom-free between relapses. One of patients had a normal intellectual outcome and cessation of symptoms at the end of follow-up (Brunklas 2011). Most retrospective studies demonstrate a similarly poor outcome with 60–80% of patients presenting neurological sequelae. A severe initial presentation predicted a chronic disease and later specific learning disabilities.

The optimal treatment of OMS is not fully established (Pranzatelli 2005; Rostasy 2006; Gorman 2010; Hero 2013), with two trials are presently ongoing. One from the Children Organisation Group tested 58 children with neuroblastoma and OMS, randomising one arm to steroids and cyclophosphamide and the other to steroids, cyclophosphamide and immunoglobulins. The second trial in Europe is an escalation from steroids alone through cyclophosphamide and rituximab, the end point being the percentage of children reaching each level of treatment. It is however suggested by uncontrolled series that early immunosuppression (either using cyclophosphamide or rituximab) is more efficient to prevent future cognitive sequelae than steroids alone.

RAPID-ONSET OBESITY WITH HYPOVENTILATION AND AUTONOMIC DYSREGULATION

Rapid-onset obesity with hypothalamic dysfunction, hyperventilation and autonomic dysregulation (ROHHAD) syndrome, also called idiopathic hypothalamic syndrome, has five
diagnostic criteria: (1) apparent normality before onset of obesity; (2) sudden onset of hypothalamic dysfunction defined by one or more of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotrophin deficiency or delayed or precocious puberty; (3) autonomic dysfunction; (4) alveolar hypoventilation; (5) absence of PHOX2B mutation. The last criterion is important to differentiate this syndrome from genetic syndromes due to mutations in the PHOX2B gene (congenital central hypoventilation gene or Ondine syndrome, late onset-central hypoventilation syndrome) (Nunn 1997; Amiel 2003; De Pontual 2008).

ROHHAD syndrome is a rare disorder and no formal natural history study has been published. The age at onset is between 1.5 and 7 years, usually with the onset of rapid obesity. Seizures are reported in a third of patients when focusing on neurological symptoms with the frequency of associated cognitive impairment varying between series and MRI being usually normal. Finally, in a recent exhaustive review 22 of 55 reported patients had an associated neural crest tumour that can be present from birth to puberty; (3) autonomic dysfunction; (4) alveolar hypoventilation; (5) absence of PHOX2B mutation. The last criterion is important to differentiate this syndrome from genetic syndromes due to mutations in the PHOX2B gene (congenital central hypoventilation gene or Ondine syndrome, late onset-central hypoventilation syndrome) (Nunn 1997; Amiel 2003; De Pontual 2008).

Management includes treatment of the neural crest tumours and symptomatic approaches. No immunosuppressive treatment analogous to what is performed in OMS is available. However, several cases of ROHHAD have been reported in association with tumors, and treatment analogous to what is performed in OMS has been published.

REFERENCES


# Accidental and Non-Accidental Injuries by Physical and Toxic Agents

*Karen Barlow, Robert Forsyth and Robert Minns*

### Acquired Brain Injury
- The Concept of Acquired Brain Injury

### Epidemiology
- Accidental Traumatic Brain Injury
- Non-Accidental (Inflicted) Brain Injury
- Non-Traumatic Coma

### Pathophysiology of Traumatic Brain Injury
- Neuroinflammation
- Biomechanics of the Primary Injury

### Common Pathologies seen in Paediatric Traumatic Brain Injury

### Clinical Assessment of Traumatic Brain Injury
- Emergency Assessment of Apparently Trivial Head Injury
- Emergency Assessment of Severe Traumatic Brain Injury

### Measures to Reduce intracranial pressure and Maintain Cerebral Perfusion Pressure

### Predictors of Outcome

### Management and Care
- Post-Concussion Syndrome and Mild Traumatic Brain Injury

### Spinal Cord Injury
CHAPTER 13

Accidental and Non-Accidental Injuries by Physical and Toxic Agents

Karen Barlow, Robert Forsyth and Robert Minns

This chapter addresses acquired traumatic, toxic and hypoxic–ischaemic causes of acute brain and spinal cord disease. The emphasis is on acquired brain injury (ABI).

ACQUIRED BRAIN INJURY

THE CONCEPT OF ACQUIRED BRAIN INJURY

An important justification for ABI as an umbrella term for a wide range of heterogeneous insults relates to service provision and planning. Services for children with additional health and education needs are largely designed for the historically greater numbers of children with developmental disabilities (including cerebral palsy [CP]). ABI characteristically causes ‘patchy’ (i.e. focal or multifocal) injuries, resulting in uneven profiles of preserved strength and new weaknesses: the very severely injured child with major new motor control problems, but relatively preserved cognition, poses a severe challenge to augmentative and assistive communication (AAC) services, or the much more common ‘invisibly injured’ profile of a young person who walks, talks and has full independence in activities of daily living, but remains very incapacitated by new executive skill weaknesses (see below).

EPIDEMIOLOGY

ABI is the leading cause of death and neurological disability in children after infancy. ABI includes the effects of central nervous system (CNS) infection (see Chapter 11), stroke (see Chapter 15) and tumours (Chapter 14); however, traumatic brain injury (TBI) is the most common cause of ABI in developed countries in childhood (Luerssen et al. 1988; Langlois et al. 2004).

ACCIDENTAL TRAUMATIC BRAIN INJURY

Comparison of incidence and mortality rates across published studies can be difficult for a number of reasons. Samples may be population or hospital admission based, prospective or retrospective, and differ in terms of severity thresholds and age limits. Traumatic brain injury (TBI) severity is typically graded using the Glasgow Coma Score (GCS) with a GCS ≤8 regarded as indicative of severe TBI (about 5% of all head trauma); GCS 9–12 indicates moderate TBI (5–10%) and 85–95% minor TBI (GCS >12) (Miller 1993).

Table 13.1 summarises some of the most recent international epidemiological studies of paediatric TBI.

These studies include rates of attendance at accident and emergency departments (A&E), hospitalisation and admission to paediatric intensive care units (PICUs). On average, 10% of children with TBI will be hospitalised, although thresholds for A&E attendance are falling with increased awareness of rare but important complications of apparently minor injury (Colvin et al. 2013). Mortality rates are low and continue to decrease. The number of children killed or seriously injured in road traffic accidents in the UK fell some 67% between 1979 and 2003, assumed to be the result of legislation and road safety campaigns, including improved car impact resilience, the compulsory use of car seats and seat belts for infants and children, traffic calming measures and speed limit enforcement, etc. Causes of TBI are listed in Table 13.2.

Falls are the most common cause of TBI and are most frequent in the first year of life (Langlois et al. 2005a; Faul et al. 2010). Preventive measures, such as safety rails, locks and modification of play equipment and surfaces in play areas, help reduce incidence and severity.

Road traffic accidents are the next most common cause and occur more commonly in the 10- to 15-year age group. It is more common for a child to be a pedestrian (36%) than an occupant of a vehicle. TBI caused by traffic accidents peaks at around 10 years of age. Accidents typically occur in late afternoon and early evening, and the rates peak in the
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Severity</th>
<th>Age range (years)</th>
<th>Period</th>
<th>Incidence (per 100,000 per year)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitra et al. (2007)</td>
<td>Population based, Australia. Retrospective</td>
<td>Mild–fatal</td>
<td>0–15</td>
<td>2000s</td>
<td>765 (all severity)</td>
<td>(All severities) five per 100,000 hospitalised; 7 ‘significant’. Mortality 1.6</td>
</tr>
<tr>
<td>Bowman et al. (2008)</td>
<td>Hospital admissions, USA. Prospective</td>
<td>Mild, moderate and severe HI</td>
<td>0–19</td>
<td>1991–2005</td>
<td>119 (hospitalised)</td>
<td>Declining 39% by 2005. Mortality declining from 3.5 to 2.8 over study period (marked reduction in admission of mild TBI during study period)</td>
</tr>
<tr>
<td>van Pelt et al. (2011)</td>
<td>Hospital based, the Netherlands. Retrospective</td>
<td>Mild–fatal</td>
<td>Children 0–14 years</td>
<td>2000s</td>
<td>130 total</td>
<td>111 ‘mild’; 5.9 ‘moderate’; 2.8 ‘severe’. Mortality 1.3</td>
</tr>
<tr>
<td>Eisele et al. (2006)</td>
<td>Hospital based, USA. Retrospective</td>
<td>Non-fatal admissions</td>
<td>&lt;2</td>
<td>1999</td>
<td></td>
<td>Bimodal age distribution with peaks at 1 month (178) and 8 months (127.9). Falls and assault more common in younger children</td>
</tr>
<tr>
<td>Hawley et al. (2003)</td>
<td>Population based, UK. Retrospective</td>
<td>Mild–fatal</td>
<td>0–14</td>
<td>1990s</td>
<td>280 all severity</td>
<td>232 ‘mild’; 25 ‘moderate’; 17 ‘severe’. Mortality 2. Children &lt;2 years = 18.8% of total. Falls account for 60% in under-5s; road traffic accidents (RTAs) most common in 10–15-year-olds</td>
</tr>
<tr>
<td>Javouhey et al. (2006)</td>
<td>Population-based registry specifically of road crash victims, France. Retrospective</td>
<td>Severe TBI from RTA</td>
<td>0–14</td>
<td>1990s</td>
<td>9.6</td>
<td>Mortality 4.3 (rate 20%)</td>
</tr>
<tr>
<td>Koepsell et al. (2011)</td>
<td>Hospital based, USA. Prospective</td>
<td>‘Medically treated’ TBI</td>
<td>0–17</td>
<td>2000s</td>
<td>304 accident and emergency (A&amp;E) attendance</td>
<td>296 ‘mild’. Combined moderate/severe/fatal 7.6</td>
</tr>
<tr>
<td>Langlois et al. (2005b)</td>
<td>Hospital based, USA. Retrospective</td>
<td>A&amp;E attendance</td>
<td>0–14</td>
<td>1990s</td>
<td>798.8 total</td>
<td>731 A&amp;E attendance; 63 hospitalised. Mortality 4.5.</td>
</tr>
<tr>
<td>Parslow et al. (2005)</td>
<td>Hospital based, UK. Prospective</td>
<td>Intensive care unit (ICU) admission</td>
<td>0–14</td>
<td>2000s</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Schneier et al. (2006)</td>
<td>Hospital based, USA. Retrospective</td>
<td>≤17</td>
<td>2000</td>
<td></td>
<td>Hospitalisation 70 (highest rates in 15–17-year-olds)</td>
<td></td>
</tr>
<tr>
<td>Reid et al. (2001)</td>
<td>Population based, USA. Retrospective</td>
<td>TBI resulting in hospitalisation or death</td>
<td>0–19</td>
<td>1993</td>
<td></td>
<td>73.5 hospitalisation. Mortality 9.3. Rates and mortality higher in non-urban areas</td>
</tr>
<tr>
<td>Meirhofer et al. (2000)</td>
<td>Population based, the Netherlands. Prospective</td>
<td>Any severity</td>
<td>0–14</td>
<td>1997</td>
<td></td>
<td>242.7</td>
</tr>
<tr>
<td>Kraus et al. (1990)</td>
<td>Hospital based, USA. Retrospective</td>
<td>Hospitalisation</td>
<td>0–19</td>
<td></td>
<td>230 hospitalisations. Mortality 10</td>
<td></td>
</tr>
<tr>
<td>Ventsel et al. (2008)</td>
<td>Estonia</td>
<td>TBI</td>
<td>0–14</td>
<td></td>
<td>369. Mortality 3.1</td>
<td></td>
</tr>
</tbody>
</table>
summer months (Parslow et al. 2005). Social deprivation is an important risk factor (Parslow et al. 2005) and Langlois et al. (2005b) reported higher rates in African-American children than white children of the same age. Kumar and Mahapatra (2009) reported that, although incidence and mortality rates have been declining for some time in developed countries, this is not the case in developing countries, where mass urbanisation means that trauma is an increasingly important cause of disability and mortality compared with ‘traditional’ factors such as infectious disease (Gore et al. 2011). Mobile phone use while driving motorbikes has emerged as a major new cause of TBI in India (Kumar and Mahapatra 2009).

Particular causes of injury are important at different developmental stages with accidents at home occurring in the first 3 years, injuries related to sport and outdoor play from 4 to 11 years, and traffic-related accidents in adolescents.

### NON-ACCIDENTAL (INFLECTED) BRAIN INJURY

Non-accidental (i.e. inflicted) head injury (NAHI), also known as abusive head trauma is the most common mechanism of head injury at age <2 years. Billmire and Myers (1985) found that in this age group 64% of all head injuries, excluding uncomplicated skull fractures, and 95% of serious head injuries were of non-accidental origin. Physical abuse constitutes about a third of all child abuse and actual brain injury is rare: it occurs in only 0.5% of all cases of abuse and 1–3% of cases of physical abuse (Minns and Brown 2005).

In the late 1990s the annual incidence of NAHI in Scotland was 24.6 per 100,000 (Barlow and Minns 2000). The median age at admission was 2.2 months (range 4 weeks to 8.8 months). A separate study estimated an incidence in south-east Scotland of 33.8 per 100,000 per year (Minns et al. 2008). A population-based study in North Carolina, USA reported an incidence in the range 14–30 per 100,000 (Keenan et al. 2003). An incidence of 14 per 100,000 has been reported in Switzerland (Fanconi and Lips 2010).

### Social Pathology and Risk Factors for Non-Accidental Head Injury

Risk factors may vary according to the region or country under study. Prospective studies have identified risk factors including alcohol and drug misuse, previous Social Services intervention, young maternal age, multiple pregnancies, past parental military service and poorer parental educational achievement. Boys are at increased risk (Goldstein et al. 1991, 1993; Keenan et al. 2003; Hobbs et al. 2005; Mok et al. 2010). An ‘index of multiple deprivation’, reflecting local income, employment, education, crime and housing factors, is a risk factor for NAHI in Scotland (Minns et al. 2008). Perpetrators experience biological, social, environmental and financial stresses, which precipitate impulsive violent behaviour, particularly if the threshold for such behaviour is reduced by alcohol or drug misuse. It has recently been shown that NAHI rates rise at times of economic recession (Huang et al. 2011).

### NON-TRAUMATIC COMA

There are many potential causes of coma of non-traumatic origin (NTC) and the aetiology remains unidentified in approximately 14% cases.

Infections are the most common causes of NTC, which includes not only meningitis and encephalitis but the indirect neurological effects of systemic (particularly respiratory) infection (Table 13.3 and see Chapter 11). Pneumococcal meningitis has declined in incidence since the availability of the pneumococcal vaccine, but still has a high fatality rate of 13%, and infection in infancy frequently has neurological sequelae. Poor prognostic signs include coma, prolonged seizures and delayed presentation (de Jonge et al. 2010).

Other causes of NTC include hypoxia–ischaemia, exemplified by cardiac arrest or near-miss sudden infant death. Out-of-hospital cardiac arrest has a very poor outcome, particularly if seizures are present. Water temperature is an important determinant of outcome after near drowning, and remarkably good outcomes can be seen after prolonged immersion in ice water (Forsyth and Kirkham 2012).

### PATHOPHYSIOLOGY OF TBI

A child’s brain is more vulnerable to traumatic injury and has a poorer outcome than the adult brain. The infant and juvenile

---

Table 13.2 Causes of traumatic brain injury

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls, 45.1%, of which:</td>
<td></td>
</tr>
<tr>
<td>From bicycle</td>
<td>5.7</td>
</tr>
<tr>
<td>From horse</td>
<td>1.2</td>
</tr>
<tr>
<td>Dropped</td>
<td>3.3</td>
</tr>
<tr>
<td>Road traffic accident, 21.1%, of which:</td>
<td></td>
</tr>
<tr>
<td>Pedestrian</td>
<td>12.7</td>
</tr>
<tr>
<td>Passengers</td>
<td>3.5</td>
</tr>
<tr>
<td>Cyclist</td>
<td>3.4</td>
</tr>
<tr>
<td>Other</td>
<td>1.5</td>
</tr>
<tr>
<td>Struck by object, 11.7%, of which:</td>
<td></td>
</tr>
<tr>
<td>Assault</td>
<td>3.5</td>
</tr>
<tr>
<td>Sport</td>
<td>2.7</td>
</tr>
<tr>
<td>Non-accidental head injury</td>
<td>2.2</td>
</tr>
<tr>
<td>Other</td>
<td>0.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Adapted from Hawley et al. (2003).
The pathophysiology of TBI is complex. A TBI results in early ionic and neurotransmitter perturbations that initiate a cascade of events that disrupt normal cellular function, including changes in glucose metabolism, free radical production and mitochondrial dysfunction. These processes are collectively referred to as excitotoxicity. (See Prins et al. 2013 for an excellent review.)

Traumatic cellular membrane perturbation and/or pore formation results in an indiscriminate release of neurotransmitters, leading to a massive efflux of potassium and sodium influx. Sodium/potassium pumps try to restore the ionic equilibrium using ATP, with a resultant high metabolic and glucose requirement. Within 6 hours, increases in intracellular calcium occur. Calcium is sequestered from the endoplasmic reticulum and imported into mitochondria, leading to mitochondrial dysfunction, oxidative stress and free radical formation.

Changes in cerebral glucose metabolism are characteristic of TBI, with initial hypermetabolism and a later prolonged period of hypometabolism. Severe injuries have the longest period of decreased metabolism, and animal studies suggest that adults have a more prolonged response than juveniles. Decreased cerebral glucose metabolism may be due to decreased cerebral blood flow (CBF), decreased glucose transporter function or decreased cellular metabolic demand. In the acute phase, a combination of reduced CBF and increased cerebral cellular metabolic demand (i.e. relative ‘uncoupling’ of the usual closely regulated link between CBF

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
<th>Period</th>
<th>Incidence (per 100,000 population per year) and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockmann et al. (2013) (Utah)</td>
<td>Laboratory-confirmed pneumococcal meningitis</td>
<td>1997–2000 vs 2001–2010</td>
<td>0.78 before and 0.57 after introduction of vaccine 63% have neurological sequelae. 13% mortality</td>
</tr>
<tr>
<td>Eskola et al. (Finland) Zangwill et al. (1996) (California)</td>
<td>Invasive pneumococcal infection</td>
<td></td>
<td>Most common cause of bacterial meningitis in the USA in children &lt;2 (equates to 45–145/100,000 children aged &lt;2)</td>
</tr>
<tr>
<td>Ahmed et al. (2011) (Karachi)</td>
<td>Non-traumatic coma resulting in paediatric intensive care unit (PICU) admission</td>
<td>2008–9</td>
<td>Infective causes have highest mortality</td>
</tr>
<tr>
<td>Wong et al. (2001) (UK)</td>
<td>Non-traumatic coma</td>
<td></td>
<td>Incidence 30.8/100,000 children; 160/100,000 infants. Infection the most common aetiology but many causes. 14% remain unknown</td>
</tr>
<tr>
<td>Donoghue et al. (2006)</td>
<td>Out-of-hospital cardiac arrest (literature review)</td>
<td>Published articles from 1966 to 2004</td>
<td>Uncommon in previously well child; 12.1% survive to discharge from hospital; only 4% are neurologically intact if there are seizures. Survival better if arrest occurs in hospital. Trauma patients had better survival and submersion injury arrests had greater survival rate (22.7%). Witnessed arrest has improved survival</td>
</tr>
</tbody>
</table>
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and metabolism) creates the potential for an energy crisis and subsequent cascades of secondary injury.

After a TBI, levels of reactive oxygen species rise and overwhelm free-radical-scavenging systems, resulting in oxidative damage. Dysfunctional mitochondria are an important source of free radical generation. These effects result in lipid peroxidation, protein nitration and DNA oxidation. Lipid peroxidation results in damage to the cell membrane and an increase in its permeability. Protein nitration and DNA oxidation impair cellular repair mechanisms. Mitochondrial impairment is important after a TBI and can result in the activation of both apoptotic and necrotic pathways, contributing to cell death. Mitochondria from immature rats show increased susceptibility to apoptosis, contributing to the vulnerability of the young brain to injury (Soane et al. 2008). Changes in mitochondrial function are potentially reversible if the post-TBI cellular energy crisis can be treated.

**Neuroinflammation**

There is strong pathological evidence for a prolonged immune response in TBI, with microglial activation, astrocyte activation and microvascular changes in the blood–brain barrier identifiable months and years after injury. This may contribute to poorer long-term outcomes especially in children (Korn et al. 2005; Ziebell and Morganti-Kossmann 2010; Ramilackhansingh et al. 2011; Shultz et al. 2012; Johnson et al. 2013). The release of ATP from damaged neurons initiates the activation of the innate immune system (predominantly quiescent microglia), resulting in the release of inflammation-promoting mediators (e.g. cytokines, chemokines, and reactive oxygen and nitrogen species). Proinflammatory processes are intended to clear the CNS of potentially harmful substances. Anti-inflammatory processes follow this, performing reparative and regenerative functions considered to be beneficial to neuronal survival. An unbalanced or prolonged inflammatory response can be harmful (Mayer et al. 2013).

**Biomechanics of the Primary Injury**

The forces experienced by the brain depend on the size and weight of the child, the height of the fall, the speed of impact, and whether the child was stationary or moving at the time of the fall. It is usually impossible to know the exact forces applied to the head, but pathologies tend to increase as forces increase. The most common forces are linear and rotational, although penetrating and compression injuries are sometimes seen.

A fall or impact injury results in unidirectional forces (impact loading) causing tissue deformation and local injury such as a skull fracture, epidural haematoma and/or underlying contusions. ‘Contre-coup’ contusion of brain tissue against the skull diametrically opposite to the site of impact is caused by wave-like force propagation through the parenchyma. The locations of contusions depend on the structure and physical properties of the interior of the skull vault, but are commonly found in the inferior frontal and anterior temporal lobes because they rest on the floors of the anterior and middle cranial fossae, respectively. As the interior skull is relatively smooth, coup and contre-coup contusions are relatively rare in infants.

Rotation of the head on the neck (inertial loading) leads to angular acceleration-deceleration forces within the skull, and is an important cause of pathology in TBI. More intracranial pathology is seen as rotational acceleration–deceleration forces rise. Injuries range from tearing of the subdural bridging veins (with resultant subdural and subarachnoid haemorrhages), to axonal and capillary shearing at the grey–white matter junction, and with the highest forces injury to the midbrain and brainstem (Ommaya et al. 2002). In vivo strain modelling using adult human MRI reveals that brain shift patterns are complex, and have high regional and inter-individual variations (Feng et al. 2010; Monea et al. 2012). The highest levels of stretch and shear are seen at the cortical surface of the brain (including frontal, superior and occipital sites), where the potential for displacement is greatest, but high levels are also seen near basal points of attachment of the brain to the skull (e.g. bony prominences, internal carotid arteries, optic and oculomotor nerves, olfactory tracts and the pituitary stalk) (Bayly et al. 2005; Zou et al. 2007). Other mechanisms of brain injury include penetrating injury (e.g. gunshot wounds), compression in road traffic accidents and abusive injuries, and blast injuries but these are infrequent in children.

**COMMON PATHOLOGIES SEEN IN PAEDIATRIC TRAUMATIC BRAIN INJURY**

The distinct biomechanics of injury in the young brain result in the potential to generate larger angular acceleration–deceleration forces. Pathologies therefore vary by age and mechanism of insult (see Figs 13.2–13.5). TBI in the infant and toddler is associated with subdural haematomas and diffuse cerebral oedema. Contusions are seen less frequently than in adult TBI. Hypoxic–ischaemic injury is frequently seen in inflicted TBI (Suh et al. 2001). Adolescents show similar injury patterns to adults, where contusions and axonal injury are the most common pathologies.

Epidural haematomas (EDHs) are almost always associated with linear forces, with or without a skull fracture. Although uncommon in TBI (1–6% of hospital admissions) an EDH is important because treatment often involves surgical evacuation (usually where the diameter exceeds 18mm and/or there is associated raised intracranial pressure [ICP]) (Case 2008). Approximately 10% of EDHs are associated with a ‘lucid interval’, followed by loss of consciousness. The outcome is usually excellent.

Subdural haematomas and haemorrhages (SDHs) are common in paediatric TBI and almost ubiquitous in infantile inflicted TBI. Nearly all SDHs are due to injury to a dural bridging vein, caused by linear or rotational forces, but can
also be seen in normal neonates probably as a result of the shift of overlapping of skull bones during childbirth (Levin et al. 1997; Whitby et al. 2004).

Diffuse axonal injury (DAI) and traumatic axonal injury are the result of shearing rotational forces. However, axons are also damaged by the secondary biochemical cascades that occur over the following hours to days. Pathological studies of DAI have revealed microscopic features corresponding to wällerian axonal degeneration. Three grades of increasing severity based on the depth of the lesions have been described, with grade 1 comprising lesions at the grey–white matter interface, grade 2 comprising additional lesions in the corpus callosum and grade 3 demonstrating further lesions to the rostral lateral–dorsal brainstem. This mirrors the findings seen in the in vivo human MRI modelling studies discussed above. It is also associated with diffuse vascular injury, hypoxic–ischaemic injury and cerebral oedema. As MRI techniques have improved, it is recognised that many similar radiological features can also be seen with milder injuries but with a much-reduced burden of injury, and the term ‘traumatic axonal injury’ (TAI) has been used for these more limited injuries.

Frontal and temporal contusions result when the brain hits bony buttresses, such as the sphenoid wing or ethmoidal plate. Parenchymal shearing and deformation injury lead to local cerebral oedema and areas of gross or petechial haemorrhage.

Cerebral oedema can be classified into two main categories: vasogenic oedema and cytotoxic oedema. Cytotoxic oedema is characterised by an increase in intracellular water content and vasogenic oedema by increased extracellular water.
Oedema results from increased intracellular osmolality. Vasogenic oedema results from disturbance of Starling forces and/or increased permeability of the blood–brain barrier (BBB). Cytotoxic oedema typically occurs later than vasogenic oedema, and typically reflects the failure of the sodium/potassium pumps (see above). Vasogenic oedema occurs early after injury but can persist for several weeks, and is an important contributor to increased ICP and secondary injury (see below). Aquaporins, matrix metalloproteinases and vasoactive inflammatory agents play an active role in regulation of BBB permeability, and are generating much interest as potential therapeutic targets for decreasing secondary injury after TBI (Donkin and Vink 2010).

**CLINICAL ASSESSMENT OF TBI**

Emergency Assessment of Apparently Trivial Head Injury

The aim of clinical assessment of children after apparently minor closed head injury is to identify those who are at risk of avoidable disability or even death. A very small proportion of these apparently well children will deteriorate in the first few hours after injury as a result of slowly expanding, space-occupying haematomas (either subdural or epidural). Untreated, the expanding haematoma causes the ICP to rise steadily, eventually risking herniation and coning (see below). Prompt identification and neurosurgical evacuation of space-occupying haematomas will dramatically improve the outcome.

The traditional approach to this triage problem was to admit children for periods of 24–48 hours of in-patient observation. However, because deterioration is a very rare event, complacency and inadequate neurological observation were a constant problem. Over the last decade or so, there has been a major change in philosophy with much greater use of early CT on admission. A child with a normal CT scan can be discharged with confidence. However, there are logistical challenges and radiation-exposure concerns about the very widespread use of CT in A&E.

Various decision rules trying to optimise the threshold for CT have been developed: they err on the side of high sensitivity (wishing to miss as few at-risk children as possible) at the expense of specificity (resulting in many normal CT scan results), and place varying emphases on clinician discretion. Box 13.1 shows the CHALICE (Children’s Head Injury Algorithm for the Prediction of Important Clinical Events) clinical decision rule (Dunning et al. 2006).

Comparisons of these rules, based on discriminatory precision (Lyttle et al. 2012; Easter et al. 2014) and health economic (Holmes et al. 2013) criteria, have been reported (Forsyth and Pearce 2013).

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**Box 13.1 Children’s head injury algorithm for the prediction of important clinical events (CHALICE)**

A clinical decision rule for requesting a CT scan in apparently minor traumatic brain injury

A CT scan is required if any of the following criteria are present

**History**
- Witnessed loss of consciousness of >5 min duration
- History of amnesia (either anterograde or retrograde) of >5 min duration
- Abnormal drowsiness (defined as drowsiness in excess of that expected by the examining doctor)
- More than three vomits after head injury (a vomit is defined as a single discrete episode of vomiting)
- Suspicion of non-accidental injury (NAI, defined as any suspicion of NAI by the examining doctor)
- Seizure after head injury in a patient who has no history of epilepsy

**Examination**
- Glasgow Coma Score (GCS) <14, or GCS < 15 if < 1 year old
- Suspicion of penetrating or depressed skull injury or tense fontanelle
- Signs of a basal skull fracture (defined as evidence of blood or cerebrospinal fluid from ear or nose, panda eyes, Battle’s sign, haemotympanum, facial crepitus or serious facial injury)
- Positive focal neurology (defined as any focal neurology, including motor, sensory, coordination or reflex abnormality)
- Presence of bruise, swelling or laceration >5 cm if < 1 year old

**Mechanism**
- High-speed road traffic accident as a pedestrian, cyclist or occupant (defined as accident with speed >40 mph)
- Fall of >3 m in height
- High-speed injury from a projectile or an object

If none of the above variables is present, the patient is at low risk of intracranial pathology
Emergency Assessment of Severe TBI

Initial resuscitation priorities are to secure the airway, and ensure adequate ventilation and circulation. Hypoglycaemia should be urgently corrected if present. Coma level should be rapidly assessed, using a young-child adaptation of the GCS where appropriate. Cervical immobilisation is important in any injury of traumatic mechanism, particularly if of high energy (e.g. road traffic accident), or if the GCS <15, or there is any neck pain or tenderness, focal neurological deficit or other clinical suspicion of neck injury. The collar should be removed only after expert neuroradiological and neurosurgical review. To avoid high radiation doses to the thyroid, some authorities recommend plain anteroposterior and lateral cervical X-rays in young children in preference to neck CT, which is the criterion standard in adolescents and adults.

In most circumstances, any child with a GCS <8 or a rapidly deteriorating GCS should be intubated and ventilated because airway control is likely to be inadequate. Intubation and ventilation should also occur when raised ICP appears probable. Prompt recognition and management of raised ICP is potentially lifesaving.

If the GCS is <12 or deteriorating, signs of raised ICP and/or herniation should be actively sought through clinical examination of pupillary and other brainstem reflexes. A dilated pupil commonly indicates third cranial nerve involvement in a herniation syndrome (Fig. 13.5) but rarely may reflect an afferent pupillary defect caused by optic nerve involvement in an orbital fracture. Papilloedema will not usually be present if the ICP has increased rapidly, but the presence of venous pulsation on fundoscopy is useful confirmation of normal ICP (although it is not seen in 10% of the ‘normal’ population). Retinal haemorrhages are pertinent in the assessment of suspected non-accidental (inflicted) injury.

Brain CT has a central role in the emergency evaluation of TBI, particularly if clinical assessment suggests a raised ICP, and should be performed as soon as initial resuscitation and stabilisation have been achieved. In the context of head trauma, neurosurgically remediable causes of raised ICP (particularly haematomas that are causing raised ICP in the rigid box of the skull because of their space occupation) should be actively sought.

Even if initial CT does not identify surgically remediable pathology, most centres would advocate invasive monitoring of ICP via a surgically implanted catheter or transducer (variously placed in the subarachnoid space, brain parenchyma or lateral ventricles), as an important component of neurosurgical intensive care. Increases in ICP in the days after injury should prompt early consideration of repeat CT in case a surgically remediable problem has developed.

Secondary brain injury refers to the phenomenon of injury additional to the direct effects of trauma. As discussed above, cascades of excitotoxicity, free radical production and energy crises are important but are not currently directly remediable. Routine clinical care currently addresses important additional causes of secondary injury, including hypoxia, hypotension, decreased cerebral perfusion and energy failure. These primarily result from systemic shock (e.g. caused by extracranial injury), primary injury to the brainstem, impaired cerebral autoregulation and increased ICP. Other mechanisms include hyponatraemia, seizures, hyperthermia, post-traumatic vasospasm, secondary haemorrhage, apoptosis and perfusion–reperfusion injury. In the infant especially, hypoglycaemia is an additional cause of secondary injury.

MEASURES TO REDUCE INTRACRANIAL PRESSURE AND MAINTAIN CEREBRAL PERFUSION PRESSURE

Differences in ICP between intracranial compartments, or in which brain structures are displaced around or through anatomical barriers, causing further compression and ischaemia (Fig. 13.6).

Subfalcine herniation under the free edge of the falx causes necrosis of the cingulate gyrus and compression of the pericallosal artery. In a tentorial herniation the medial temporal lobe (uncus) shifts through the tentorial hiatus. This results in uncal infarction and compresses the blood supply to the midbrain and brainstem, causing midbrain infarction and haemorrhages (Durant haemorrhages). It can also compress the posterior cerebral arteries, causing focal ischaemia of the calcarine cortex and resulting in cortical blindness.

If a raised ICP is not relieved, descent of the brainstem and cerebellar tonsils causes impaction, and coning occurs at the foramen magnum. This can cause secondary ischaemia of the medulla and upper cervical cord, as well as cerebellar tonsillar necrosis and compression of the posterior inferior cerebellar arteries. The clinical picture of the various shifts and cones is described later. They are important causes of secondary brain injury.

Cerebral perfusion pressure (CPP) is calculated as the difference between mean arterial pressure (MAP) and ICP, and reflects the pressure difference available to drive blood into the intracranial cavity. Inadequate cerebral perfusion can set up a
vicious cycle of cerebral ischaemia, worsening cerebral injury and oedema, further increases in ICP, decreased cerebral perfusion and further ischaemia. This occurs even in the absence of cerebral shift or herniation.

As the ICP rises, the CPP falls and, although derangements in both are associated with poorer outcome, the specificity and sensitivity of the CPP as a predictor of poor outcome are superior to those of the ICP (Chambers et al. 2006). Age-specific norms are available (Chambers et al. 2005) and the duration and severity of derangements predict the outcome (Jones et al. 2003). Chambers et al. (2005) suggest that the CPP should be maintained above 53mmHg in 2–6-year-olds, 63mmHg in 7–10-year-olds and 66mmHg in 11–16-year-olds. International guidelines (Kochanek et al. 2012) suggest a target CPP of 40–50mmHg. The outcome relates to both the magnitude and the duration of the ICP/CPP derangement and cumulative pressure–time indices have been developed (Jones et al. 2005). The optimal CPP for a given patient will depend on cerebrovascular autoregulatory capacity, and will, therefore, probably vary between patients and with time post-injury. Estimation of the optimal CPP measured from high temporal-resolution physiological data has been demonstrated as a research technique, but is not yet in routine clinical use (Guiza et al. 2013). The ICP/CPP data are most likely to influence neurosurgical management decisions in the first 6 hours after injury.

Measurement of the oxygen saturation of internal jugular venous blood returning from the brain (\(S_JVO_2\)) by an electrode placed at the jugular bulb provides a direct measurement of whole-brain oxygen extraction and thus adequacy of brain oxygenation. \(S_JVO_2\) should be kept between 54% and 75%. Lower values indicate cerebral olighaemia, and higher values, cerebral hyperaemia. Direct jugular venous blood sampling can be combined with arterial blood sampling and/or techniques measuring whole-brain CBF to allow calculation of arteriovenous oxygen differences and cerebral metabolic rates. However, the invasiveness of these techniques discourages their routine clinical use.

A comprehensive review of the best available evidence for the management of increased ICP can be found in the Guidelines for the management of severe TBI in children (Kochanek et al. 2012). Medical management of raised ICP includes nursing with the head in midline and tilted up 30° and avoiding unnecessary handling and suction (coughing raises intrathoracic pressure and thus ICP). Cerebral arterioles dilate under conditions of hypercapnia. Past policies of hyperventilation intended to induce hypocapnia, and thus vasoconstriction, certainly reduce ICP; however, the inadvertent ischaemia is now known to worsen outcomes; ventilation to normocapnia with temporary manual hyperventilation in the presence of spikes of raised ICP is now conventional. A similar balance needs to be struck between maintenance of an adequate circulating volume and avoiding cerebral oedema through fluid overload. Boluses of mannitol may be useful in the short term for managing spikes of raised ICP, but eventually become counterproductive (as mannitol eventually elevates intracellular osmolality), and again careful attention to fluid balance after the bolus (avoiding hypovolaemia) is required because it acts as an osmotic diuretic. Obvious seizures will cause raised ICP again and should be treated. However, routine use of prophylactic anticonvulsants is not recommended except in cases of non-accidental injury and infantile TBI, or where there is

Figure 13.6 Brain herniation patterns: (1) subfalcine (also known as cingulate); (2) central; (3) uncal; (4) tonsillar; (5) upward cerebellar (seen with posterior fossa lesions, leading to impingement of the posterior cerebral arteries); and (6) transcalvarial (may occur with skull fracture or at craniectomy sites).
substantial intraparenchymal haemorrhage (Kochanek et al. 2012; Arndt et al. 2013).

Although, hypothermia offers neuroprotective benefit in neonatal asphyxia no benefit has as yet been demonstrated in paediatric TBI (Hutchison et al. 2008). The benefit of other neuroprotective strategies including corticosteroids (Roberts et al. 2004) is also unclear. Hyperthermia should be avoided, although it is not clear whether fever is a risk factor for poor outcome caused by hyperthermia itself or secondary injury associated with neuroinflammatory processes (Bao et al. 2014).

In severe, resistant, raised ICP, surgical approaches may be important. If ICP monitoring is being performed via a ventricular catheter then cerebrospinal fluid (CSF) drainage may be possible at least until the ventricles have completely effaced. There is renewed interest currently in decompressive craniotomy (removal of skull vault bones to allow unrestricted brain swelling). However, evidence of benefit is lacking in both children (A Taylor et al. 2001; Cooper et al. 2011) and adults (Cooper et al. 2011; Sahuquillo et al. 2013).

General Supportive Measures

Electrolyte imbalances can occur as a result of cerebral salt wasting, diabetes insipidus and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and should be monitored frequently. Paroxysms of sympathetic hyperactivity with hypertension, fever and hyperhidrosis (sometimes known as dysautonomia) are frequent after severe TBI, often occurring at emergence from a coma, and can be very troublesome. Strategies to treat these should be aggressive because they are distressing for families to witness, and the resultant hyperpyrexia and rhabdomyolysis are a potent cause of renal and renal kidney failure. Management strategies include sympathetic blockade using beta blockers such as propranolol (Cotton et al. 2007), and/or centrally acting alpha2-agonists (e.g. clonidine) (Nordström 2005).

Tracheotomy may be necessary if prolonged ventilation is required. Care should be taken during the prolonged periods of immobility of neurointensive care to prevent pressure sores and the development of contractures, particularly restriction of foot dorsiflexion. Critical care neuropathy and myopathy can also occur in children with prolonged intensive care unit (ICU) admissions.

Non-Accidental (Inflicted) TBI

The forensic evaluation of suspected NAHI is outside the scope of this chapter. Secondary hypoxic injury is common and cerebral oedema can be severe. Acute management of seizures can also be challenging, although these typically abate after a few days. Mortality and late morbidity rates are high.
**PREDICTORS OF OUTCOME**

**Determinants of Outcome of TBI**

Outcomes from TBI may be considered globally or in terms of specific domains (Forsyth 2008). Global outcome measures include the Glasgow Outcome Scale (McCauley et al. 2001) and a paediatric equivalent – the King’s Outcome Scale for Child Head Injury (KOSCHI) (Crouchman et al. 2001). Domain-specific instruments assess constructs including functional independence, health-related quality of life, neuropsychological domains (e.g. intellectual, adaptive, executive and social function) and measures of gross motor function (McCauley et al. 2012).

Outcomes after TBI are predicted by pre-injury demographic factors, injury-related factors and post-injury factors (Johnson et al. 2009) and are summarised in Table 13.4. Pre-injury demographic predictors include age, prior intellectual ability, the presence of behavioural or psychiatric conditions, socioeconomic status and family dynamics. Post-traumatic injury predictors include success with rehabilitation programmes and interventions. Some rehabilitation techniques improve cognition and behaviour. Integrated and multidisciplinary assessment and coordination of care as part of the rehabilitation improve the overall quality of life for the individual and his or her family.

The long-term impairments after paediatric TBI include behaviour, neuropsychological function (attention, executive function, memory, speed of processing), skills of activities of daily living (ADL), social skills, psychological status and quality of life. An early, impaired memory ability is indicative of persistent problems 2 years later and the need for special education (Miller and Donders 2003). The pattern of interaction between child behaviour problems and family functioning 6 months post-injury is extremely predictive of the burden on the family, parental stress and child behavioural problems at 1 year (HG Taylor et al. 2001b).

**Predictors of Outcome after Non-Traumatic Brain Injury**

Outcomes after postnatal hypoxic–ischaemic encephalopathy (HIE) are typically poorer than after TBI (Heindl and Laub 2007). They correlate with injury severity (e.g. duration of unconsciousness) (Kriel et al. 1994). Other predictors of poor outcome (death and vegetative state) after postnatal HIE include hypoglycaemia, absent pupillary light reflexes, epileptic seizures, cardiopulmonary resuscitation for more than 10 minutes, and abnormal EEG and brain imaging. The predominance of injury severity in predicting outcome leaves little room for post-injury factors to influence outcome, because pre-injury factors, younger age and ethnicity have been associated with a better outcome (Lee et al. 2006).

Outcome from near drowning is typically bimodal with either relatively intact recovery or death or a vegetative outcome. Immersion in ice-cold water can be protective and associated with a good outcome; warmer temperatures are associated with a worse outcome. Less severe anoxic events may be associated with localised brain lesions and corresponding deficits, for example, of the hippocampus and subsequent memory impairment (Hopkins and Haaland 2004).

Outcome after stroke is determined by type, extent and location of the lesion. Haemorrhagic stroke is more frequently fatal than ischaemic stroke, and seizures are usually a marker of poor global outcome. The size and location of an arteriovenous malformation predicts outcome (Pasqualin et al. 1991). A young age at the time of the stroke will result in a worse global outcome and poor language development (Ganesan et al. 2000; Chapman et al. 2003).

For infectious encephalitides, coma at presentation, repeated seizures and duration of illness are all associated with a poor outcome. The type of encephalitis is also important: Japanese B and herpes simplex virus, and tick-borne encephalitis with optic nerve involvement, are all associated with significant sequelae. Age is associated with a poor outcome in children with bacterial meningitis (Pentland et al. 2000).

For a more detailed review see Forsyth and Kirkham (Forsyth and Kirkham 2012).

**Age at Injury**

The effect of age at injury on outcome is debated in the paediatric ABI literature. Impressions that young children make better recoveries from brain injury than adults would be expected to are commonplace, but over-simplify a complex picture. Contradictory messages come from literature looking at different domains of outcome after different types of injury. The most optimistic views come from the literature on language outcomes after very early unihemispherical injury: it is clear that language can relocate to contralateral structures, if they are unaffected, with remarkable efficiency (Vargha-Khadem et al. 1997). Such flexibility in localisation may be less possible for domains such as vision and motor function, the ancient evolutionary origins of which are reflected in specialised local cortical microstructures.

TBI is typically diffuse and multifocal. Children tend to make better motor recoveries after TBI than might be expected in adults; however, any advantages of greater plasticity in the immature nervous system need to be balanced against the fact that development is not yet complete and must be completed with an injured brain. It follows that what must be meant by ‘full recovery’, in the context of paediatric ABI, is not just a return to pre-injury levels of function, but completion of development without prejudice. In very simplistic terms, motor function (‘walking’) is largely established by the start of formal schooling and language function (‘talking’) by the end of primary schooling, but important cognitive milestones (‘thinking’) continue to be established throughout adolescence, and indeed into the third decade of life. This is the basis for the common problem, particularly after TBI of ‘invisible'
Table 13.4 Predictors of outcome after traumatic brain injury

<table>
<thead>
<tr>
<th>Injury factors</th>
<th>Predictive physiological and imaging factors</th>
<th>Predictive biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glasgow Coma Scale (GCS) score</strong></td>
<td><strong>Subdural haemorrhage; midline shift; pulsatility index (Husson et al. 2010)</strong></td>
<td><strong>S100β + L-selectin (Lo et al. 2009):</strong> area under the curve (AUC) 0.98; specificity and sensitivity for unfavourable outcome 96% and 100%, respectively</td>
</tr>
<tr>
<td>Husson et al. (2010): severe (GCS 3–8) – higher risk of mortality (20% with GCS &lt;8 died; 0% death with GCS &gt;8)</td>
<td>Diffuse axonal injury (Galloway et al. 2008): predicted outcome 6 months after TBI</td>
<td>S100β + interleukin (IL)-6, i.e. brain-specific protein and inflammatory marker (Lo et al. 2009): AUC 0.98</td>
</tr>
<tr>
<td>GCS score 3–5 was threshold below which poor outcome was probable</td>
<td>Increased diffusion-weighted values – poor outcome at 6–12 months</td>
<td>Coma Scale + biomarkers (Lo et al. 2011): enhances prediction of unfavourable outcome in children with brain trauma</td>
</tr>
<tr>
<td>GCS score: severe – survivors – increased behavioural, educational (memory, IQ, reading, spelling) and social impairment burden, which persists</td>
<td>Secondary injuries: intracranial pressure (ICP), seizures, fever, fluctuating blood pressure (BP)</td>
<td>Paediatric intensive care unit discharge-summated GCS: AUC 0.95, predicts unfavourable outcome</td>
</tr>
<tr>
<td>Time to follow commands/Functional Independence Measure (Forsyth 2010): increased in those with cognitive impairments</td>
<td>Seizures are good predictor (Murdoch-Eaton et al. 2001)</td>
<td>Post-resuscitation summated GCS + day 1 serum IL-8: AUC 0.98, predicts unfavourable outcome</td>
</tr>
<tr>
<td>Post-traumatic amnesia (McDonald et al. 1994): sensitive predictor of memory and learning, up to 1 year. ‘Return to orientation in time place and person’</td>
<td>Complex EEG analyses (Nenadovic et al. 2008)</td>
<td>GOS (1–3, unfavourable outcome) (Lo et al. Abstract 2011): worst CPP found in this group was &gt;35mmHg below age-related CPP threshold</td>
</tr>
<tr>
<td>Open head trauma: multiple skull fractures – eight times more cognitive/physical disability</td>
<td>ICP and cerebral perfusion pressure (CPP) (Carter et al. 2008): associated with increase mortality and morbidity</td>
<td>Above patients had increased levels of S100β (P=0.001) + L-selectin (P=0.024) and IL-8 (P=0.034)</td>
</tr>
<tr>
<td>Infants and non-accidental head injury (Brenner 2003): increased secondary injury; more cognitive deficit than acute traumatic brain injury (TBI)</td>
<td>Duration of age-specific derangement of CPP (Jones et al. 2003): found to predict outcome (dead vs alive: P=0.003 and Glasgow Outcome Scale (GOS) 1–3 vs GOS 4–5, i.e. poor versus independent outcome, P=0.004)</td>
<td>S100β highest predictive value for CPP insult depth (AUC = 0.95)</td>
</tr>
<tr>
<td>Family supported rehabilitation (Braga et al. 2005)</td>
<td>Impaired autoregulation of BP: poor outcome</td>
<td><strong>S100β, neuron-specific enolase (NSE), myelin basic protein (Berger et al. 2010)</strong></td>
</tr>
<tr>
<td><strong>Predictive biomarkers</strong></td>
<td>Episodic hypo-/hypertension in first 24 hours: poor outcome</td>
<td><strong>Continued</strong></td>
</tr>
<tr>
<td>S100β + L-selectin (Lo et al. 2009): area under the curve (AUC) 0.98; specificity and sensitivity for unfavourable outcome 96% and 100%, respectively</td>
<td>SEP and motor responses (Carter and Butt 2005)</td>
<td><strong>S100β, neuron-specific enolase (NSE), myelin basic protein (Berger et al. 2010)</strong></td>
</tr>
<tr>
<td>S100β + interleukin (IL)-6, i.e. brain-specific protein and inflammatory marker (Lo et al. 2009): AUC 0.98</td>
<td>Motor component and pupillary responses have prognostic value (Cassidy et al. 2003): best predictor of poor outcome</td>
<td><strong>Continued</strong></td>
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</table>
injuries in children whose good motor recoveries belie the significance of their cognitive morbidity, which becomes steadily more evident with passing years. Under-recognition and non-attribution of late cognitive effects to prior TBI are a common problem (Forsyth 2010).

**MANAGEMENT AND CARE**

**Educational Provision**

ABI often results in focal or multi-focal brain injury, reflected in ‘uneven’ cognitive profiles with areas of relatively specific weakness and islands of preserved ability. This may create an immediate challenge to return to school, for example, in the situation of a child with severe new problems with voluntary movement control (which would typically also involve speech production), but relatively preserved understanding and cognition. Many children with motor control impairments of similar severity that are of developmental origin (e.g. caused by severe CP) would typically also have severe learning difficulties; however, such a school environment may be totally unsuitable for an older ABI survivor with similar levels of motor impairment. Specialist AAC support is likely to be crucial in such situations. Expressive communication (making oneself understood) ultimately requires the ability to perform movements when wished (and to be relatively free of unintended occurrences of the same movement). AAC approaches rely on identifying the remaining voluntary movements that are most suitable for accessing switching devices to operate communication systems.

Immediately evident consequences of ABI may also include new sensory impairments of vision or hearing. The highly specific and sometimes bizarre sensory and cognitive impairments sometimes reported in adult case literature after an extremely localised stroke (e.g. affecting facial recognition or perception of movement, auditory perception of pitch or timing in sound or even changes in spoken accent) generally arise from perforator artery stroke as a result of atherosclerosis, and are very rare in children. Most educational and behavioural effects of ABI are in high-level cognitive functions and tend to emerge slowly over the years after injury. Particularly after TBI the inferomedial temporal and inferior frontal lobes structures are vulnerable as a result of their proximity to the bony floors of the middle and anterior cranial fossae. Injury to frontal lobes results in difficulties in executive function and socioemotional communication. The term ‘executive function’ is a shorthand for the large number of skills necessary for ‘taking responsibility for one’s own life’ – the self-direction and self-organisation of adulthood. The recognition of such difficulties is often delayed, because until mid- to late-adolescence the affected areas are developmentally silent. Thus, the effects of early injury to frontal lobe structures supporting executive function may remain latent until later adolescence, when expected maturation and manifestation of such abilities fail to occur.

Injury to hippocampal structures reduces new learning efficiency. As an oversimplification, knowledge and skills learned before injury remain largely intact, but children gradually fall behind in new learning (‘not making a year’s progress every year’). These nuances complicate the delivery of informed educational provision for children after an ABI, which is perhaps the single most effective rehabilitation intervention possible. They also complicate issues of appropriate assessment. Even if teaching staff suspect that a child’s problems relate to earlier ABI and request specialist psychological assessment, an uninformed assessment will miss the issues. Much educational assessment is performed on the basis of attainment of accrued abilities (e.g. in literacy and numeracy) over an entire educational career to date. In the case of recent injury, a large proportion of that educational career was completed with an uninjured brain; it will take many years of poorer-than-expected progress until this is reflected in a failure to have achieved age-related expectations. Assumption of a child’s ability to recognise commonalities between multiple examples and to generalise these to new examples is a basic pedagogical approach. Unfortunately, it is a frontal lobe skill that may be specifically impaired so having to explicitly teach this is an unfamiliar challenge to most teachers. Similarly, failure to appreciate the ways in which problems can emerge with time, late after injury, results in under-recognition. Regrettably, it is still all too common for the fact that an injury that occurred

**Table 13.4 Predictors of outcome after traumatic brain injury (continued)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>NSE (Bandyopadhyay et al. 2005)</td>
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<tr>
<td>S100β (Berger et al. 2006)</td>
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<tr>
<td>Glial fibrillary acidic protein (Bembea et al. 2011); strong relationship of trajectory with outcome – high specificity for prediction of poor outcome from high-risk trajectories</td>
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Predictive genetic factors

Apolipoprotein E gene on chromosome 19 (Lo et al. 2009): adverse influence of CPP levels of ApoE4 carriers with poor outcome significantly less than non-ApoE4 carriers ($P=0.03$)

Homozygotes for E3 (i.e. protective) with good recovery did so despite having 26 times more CPP insult than those who were not e3 homozygotes ($P=0.02$)
while the child was at primary school may not even be conveyed to high school staff, on the basis that the child was thought to have ‘recovered’ and the incident is erroneously presumed to be closed. A great deal of information is available to inform the educational remediation of ABI: the challenge is to recognise what is being seen and to make this information available at the right time.

There are important links between executive functions and attention control. Attention control refers to the ability to optimally sustain attention, avoiding the twin extremes of distractibility and the less recognised, but equally disruptive, problem of perseveration or over-fixation on topics – so-called ‘secondary attention-deficit–hyperactivity activity (ADHD)’, that is, deficits of attention and concentration resulting from traumatic injury to the frontal lobes are common.

**Behavioural and Forensic Issues**

Social–emotional communication is an important issue, particularly after TBI. Survivors struggle to recognise nuances of irony or sarcasm, misreading social situations and interpreting comments over-literally. They may also be unacceptably blunt and unreserved in expression of their own thoughts (Dennis 2010). Misinterpretation of a comment meant in jest, combined with impulsivity, may result in a physical over-reaction and escalation of a situation, for example possibly even resulting in involvement in the criminal justice system. A recent systematic review estimated the prevalence of past TBI in the offender population to be an astonishing 60% (Shiroma et al. 2010). The causes of this association are undoubtedly complex: children from socioeconomically deprived backgrounds are at greater risk of TBI, as are children with prior psychiatric morbidity such as ADHD (Max et al. 2004) so the occurrence of a TBI event and involvement with criminal justice systems may be independent effects of the same prior causes. However, the ‘coping style’ of the family to which a child returns after TBI is also an important, addressable mediator of late outcomes (Yeates et al. 1997). New educational difficulties may be another important, potentially preventable part of a collapse of self-esteem which may contribute to late behavioural problems.

There is much debate in the psychological literature about the relative value of attempts to retrain cognitive skills on an individual basis versus environmental optimisation (e.g. creating an informed school environment for the child). The evidence base in relation to cognitive restorative therapies is currently limited (Slomine and Locascio 2009). Trials show definite, if modest, effects but the extent to which these benefits generalise to daily function beyond the specific trait practised still has to be established. What is clear is that effective rehabilitation needs to be ecologically valid (i.e. delivered in meaningful contexts, such as school), and that appropriate peer contact is very effective in modelling and providing feedback in emotional and social competence.

**Treatment**

The mainstays of support after ABI are the provision of an informed and optimised educational environment and an empowered family. Helping a family become informed partners in the rehabilitation of, and advocates for, their brain-injured child is highly effective. However, it is also important to plan ahead to the time when the ABI survivor becomes an adult, where the goal will be as much personal independence as possible; a rehabilitation and care package that ties a young person to the family home will not be in his or her long-term interest.

Expert neuropsychological assessment is a vital component of follow-up and support after ABI to allow the parsing of an often complex picture of strengths, and sometimes surprising weaknesses, into a consistent profile of impairments in attention, new learning, executive function, and any other specific sensory or cognitive deficits. Such an understanding is an essential precursor of educational provision.

Psychopharmacological treatment of attention deficit with stimulant medication (e.g. methylphenidate) may be important. Some authorities also advocate the use of carbamazepine and/or valproate for mood-stabilisation effects.

**POST-CONCUSSION SYNDROME AND MILD TRAUMATIC BRAIN INJURY**

One in seven children will have post-concussion syndrome for 3 months or more after a mild TBI (Barlow et al. 2010). Post-concussion syndrome (PCS) is a symptom complex with a wide range of somatic, cognitive, sleep and affective features, and is the most common consequence of TBI (Blume and Hawash 2012) making it a significant public health issue because one in five children will sustain a TBI by the age of 16 years (Mckinlay et al. 2008). PCS is associated with significant disability in the child and for his and her family, and yet there are few evidence-based medical treatments available (Gagnon et al. 2005; Moran et al. 2012; Watanabe et al. 2012; Schneider et al. 2013). There is substantial controversy caused by a lack of consensus with regard to diagnostic criteria, the presence of symptoms seen commonly in the normal population, the contribution of sociological, psychological and medico-legal factors to outcomes, and, until recently, a failure to identify any abnormal pathophysiology (Meares et al. 2011).

The diagnostic criteria of the DSM-IV (APA 1994) are as follows: (1) history of TBI; (2) evidence from neurobehavioural testing of cognitive deficits in attention and/or memory; (c) three or more of the following symptoms that appear after injury and persist for 3 months or more: fatigue, headaches, dizziness, sleep disturbance, irritability, apathy or affective disturbance, or personality changes; with (4) symptoms in (2) and (3) starting or worsening after injury; (5) interference with social or occupational functioning; and
(6) symptoms that are not better explained by other mental disorders. The symptom onset must be contiguous with TBI, distinguishable from pre-existing conditions and of a minimum 3-month duration. In practice, the DSM-IV is usually modified because most physicians do not have access to neurobehavioural testing, and in any case standard neuropsychological tests are usually normal by 3 months post-injury, even though patients continue to complain of cognitive deficits (Boake et al. 2005; CP Carroll et al. 2012). Furthermore, in our experience, cognitive deficit is not a universal complaint among children and adults with PCS. We have proposed a modified paediatric definition as follows: (1) a history of mild TBI with an onset of symptoms or signs within 72 hours of the injury; (2) the presence of at least three of the following: headache, dizziness, fatigue, irritability, insomnia, difficulty concentrating, memory problems, emotional lability and mood disturbance; (3) symptom duration for at least 4 weeks post-injury; and (4) symptoms that are not better explained by another disorder (Barlow 2016).

**Epidemiology**

The incidence of PCS varies according to the diagnostic criteria used, time post-injury, age, injury severity, presence of assault and the population studied. PCS incidence rates at 1 month post-injury vary between 24.5% and 52.5% in the A&E population follow-up (Barlow et al. 2010; Pickering et al. 2012). Symptom prevalence decays exponentially with time (Fig. 13.8).

Three months post-injury, 11% of all children and 14–29% of school-aged children remain symptomatic (Barlow et al. 2010; Babcock et al. 2013); 2% remain symptomatic at 1 year (Vanderploeg et al. 2005).

**Predictors of Recovery**

Many factors are important contributors to symptom persistence, including injury severity, previous TBI, and premorbid sociological and psychological factors, as well as the presence of medico-legal issues (e.g. litigation, assault). Improvements in research methodologies have enabled researchers to gain a better understanding of these factors at various time points in recovery (Satz et al. 1997; McNally et al. 2013).

Injury severity is a significant factor in predicting acute outcomes after mild TBI, that is, up to 3 months post-injury in A&E cohorts (Mittenberg et al. 1993; Barlow et al. 2010; HG Taylor et al. 2010a; McNally et al. 2013). Severity factors include loss of consciousness, amnesia, admission to hospital, degree of the acute symptoms and the presence of other injuries (Barlow et al. 2010; Babcock et al. 2013; McNally et al. 2013). Adolescents are more likely than younger children or adults to develop PCS (Barlow and Minns 2000; Babcock et al. 2013). No predictive genetic factors have been identified (Terrell et al. 2008; Moran et al. 2009; Smyth et al. 2014).

The relative contribution of injury factors to PCS decreases over time and premorbid factors become important factors influencing symptom persistence (McNally et al. 2013; Olsson et al. 2013; Brooks et al. 2014). Some 3–6 months post-injury, premorbid child and family factors, such as school difficulties, parental pre-injury anxiety, coping strategies, adverse life events and stressors, make increasing contributions to persistent PCS symptoms, and injury-related factors are less important. Children with lower IQs and premorbid learning difficulties such as attention-deficit disorder are more likely to be injured and are prone to PCS, perhaps due to differences in cognitive reserve capacity (Fay et al. 2010). Thus, when evaluating and treating children with persistent PCS, clinicians should pay close attention to factors that may elicit symptoms for reasons other than an underlying brain injury (Kirkwood et al. 2008).

**Controversies**

PCS has been a highly debated and questioned entity for several reasons, including absence of symptom specificity, premorbid influences on outcome, recall bias, and the influence of sociological and psychological factors. The symptoms of PCS are not specific to PCS alone but are present in populations with and without disease (e.g. depression, chronic pain, anxiety) (Chan 2001; Iverson and Lange 2003; Fear et al.
2009) and involvement with litigation influences symptom reports (Lees-Haley et al. 2001; Greiffenstein and Baker 2008). When this is combined with the absence of an objective diagnostic test (at least in the chronic state), many begin to question the validity of PCS as a diagnosis. Furthermore, the cognitive and behavioural symptoms are often not prominent complaints acutely after mild TBI but emerge between 1 and 3 months post-injury, perhaps leading to the misconception that the whole condition was solely due to a mood disturbance (LJ Carroll et al. 2004; Yang et al. 2007; Dikmen et al. 2010).

Pathophysiology of PCS

There are relatively few neuroimaging studies to provide insight into the pathophysiology of PCS in children. Conventional MRI is usually normal acutely (80–90% of MR images in acute mild TBI) and almost all conventional MR images are normal in PCS. However, special imaging techniques are beginning to provide objective evidence of cerebral dysfunction. Diffusion tensor imaging (DTI) may reveal abnormalities that correlate with PCS symptoms and cognitive outcome (Wozniak et al. 2007). Common sites of DTI abnormalities are in the corpus callosum, frontal white matter and internal capsule (Henry et al. 2011; Wilde et al. 2011; Shenton et al. 2012). Children and young adults show increased activation of multiple cortical networks during working memory or spatial memory functional MRI tasks, even though the performance on the task is similar to that of a comparison group (Slobounov et al. 2010; Krivitzky et al. 2011; Wilde et al. 2011). This suggests decreased cortical network efficiency and may explain why children with PCS are so fatigued after a full day of school and complain that it is harder to perform cognitive tasks. Transcranial magnetic stimulation (TMS) can measure discrete cortical functional areas, offering non-invasive, painless mapping of motor systems. TMS has demonstrated evidence of acute and long-term cortical excitability in the primary motor cortex neurophysiology (Chistyakov et al. 1998, 2001; De Beaumont et al. 2009).

Clinical Assessment of PCS

A comprehensive assessment is necessary to evaluate a child with PCS and it should pay particular attention to risk factors for poor recovery and mimics of PCS. The differential diagnosis includes headache disorder, cervical injury, anxiety, depression, somatisation, cervical injury, vestibular dysfunction and visual dysfunction.

The history and examination should assess the following:

- Pre-injury details including factors indicating severity of injury, presence of litigation and mechanism of injury (e.g. high velocity/energy insult, elite athlete, assault)
- Medication use (screening for medication overuse), alternative therapies, use of other substances, for example, marijuana
- Current activity, for example, type and amount of exercise especially weight training and boxing
- Past medical history, for example, migraine, exercise-induced headaches, previous concussion and time taken to recover
- Pre-existing traits or disorders, for example, anxiety, depression, current learning difficulties and/or attention deficits
- Family history, for example, migraine, hemiplegic migraine, depression, anxiety
- Psychosocial history, for example, recent stressors such as loss of a family member or friend, change of school, conflicts with friends/family
- Evidence to support cervicogenic headache
- Vestibular dysfunction (using the head impulse test, Dix–Hallpike manoeuvre or a dynamic visual acuity deficit) and balance abnormalities.

Questionnaires to explore current symptoms as well as function are very useful, for example, Post Concussion Symptom Scale (Lovell and Collins 1998) and Rivermead Post Concussion Questionnaire (Eyres et al. 2005). A quality-of-life measure, for example, PedsQL (Zonfrillo et al. 2014), can also be useful to assess overall function. Other useful tools include a headache diary, and questionnaires to explore mood, anxiety and sleep dysfunction.

Investigations do not play a large role in PCS. Laboratory investigations should be considered where there is concern for endocrine dysfunction. After 2–3 months, hypersomnia is unusual and raises concerns for other medical disorders (e.g. hypothyroidism, anaemia, depression, idiopathic hypersomnia). Neuroimaging is generally not warranted. Specialised clinics may offer dynamic balance assessments as well as computerised assessments of vestibular and cognitive function, but their use in persistent symptoms has not been validated.

Management of PCS

PCS is managed somewhat differently from the acute and subacute phases after mild TBI. Rather than a focus on rest, it switches to strategies to improve general functioning, increase ADL and return the child to school. This is done in a graduated fashion, supporting the child/adolescent in his or her environment. Prolonged absence from school is not recommended and should not be longer than 2–4 weeks because this often leads to more problems when the child becomes isolated from his or her peers and loses self-confidence. Often adolescents need significant reassurance and encouragement in this process, especially when their symptoms have been present for several months.

Once the clinician has a clear understanding of the various factors contributing to symptom persistence, it is advisable to address one or two of the most problematic symptoms, and the other symptoms will often improve. Participation in school and social activities should be encouraged while this occurs. Referral to a specialist should be made for children with persistent vertigo and balance problems, or
persistent visual complaints. Peripheral vestibular dysfunction should be treated with specialised physiotherapy initially; migrainous vertigo may be treated with prophylactic agents for migraine (Alsalameh et al. 2010; Schneider et al. 2013). Convergence insufficiency and persistent reading dysfunction may respond to oculomotor neurohabilitation (Thiagarajan et al. 2014). The most common problems are, however, usually sleep disturbance, headaches, and cognitive and mood disturbances. Addressing sleep disturbance is usually the first step. As sleep improves, children find it easier to cope at school and often the mood disturbance will also improve.

Sleep Disturbance

Although sleep problems are a major concern for children and their parents, there are few studies exploring this (Blunman et al. 2009; Chapat et al. 2009; Schatz et al. 2011). Persistent PCS sleep disturbance is associated with lower sleep efficiency, more wake time and more nocturnal awakenings when assessed using polysomnography (Kaufman et al. 2001). The pathogenesis for sleep disturbance is multifactorial and correlates with increased abnormalities on MRI (Datta et al. 2009; Yaeger et al. 2014). The clinician should always examine other factors that affect sleep including sleep hygiene, pain, anxiety and depression (Gosselin et al. 2010). Medications that interfere with sleep (especially those used to treat any concomitant attention problems) should be examined, as well as the use of illicit substances and caffeine.

Mood Disturbances Following TBI

A range of psychiatric problems can be seen after TBI in children, including anxiety, depression, personality change disorder, post-traumatic stress disorder, ADHD and substance abuse. Mood disturbance is common after any traumatic injury in the first few weeks (Mainwaring et al. 2010), and occurs in up to 36% of children with mild TBI within 6 months of injury. A multidisciplinary team including a psychiatrist is necessary to manage severe depression or anxiety in childhood after mild TBI. Any sleep and pain disorders should be concurrently managed and should not delay psychiatric treatment.

COGNITIVE DIFFICULTIES FOLLOWING TBI

Whether neuropsychological impairment can persist in paediatric mild TBI is still debated. Satz et al. (1997) found no adverse effects on academic–psychosocial outcome across the spectrum of mild TBI in a comprehensive systematic review. However, children who sustain complicated mild TBI may have subtle deficits on long-term follow-up (Babikian et al. 2011). In clinical practice, where the baseline neuropsychological function is not available, the value of neuropsychological testing is unknown. Neuropsychological evaluation is useful for identifying pre-existing learning difficulties and attention problems that were ‘unmasked’ by a mild TBI. Although there is currently little evidence to support the use of stimulants for secondary attention deficits, a trial of stimulants is probably warranted. Drugs such as memantine are not warranted in PCS (especially outside a clinical trial), given the good long-term prognosis.

Return to School

Supporting children as they return to school, regardless of the time post-injury, is key. Parents and adolescents should be encouraged to talk to the school before their child returns and an individual educational plan should be developed. Where possible, exemptions should be made so that the student does not have to ‘catch up’ on all assignments or work missed, but instead priority projects or key areas should be identified. Exemption from examinations and tests should be made during the first phase of return to school, and accommodations such as a quiet environment for taking tests should be arranged. A gradual return to full participation is recommended. Sometimes psychological support is necessary during this time, especially if plans for graduation or university hopes have to be put on hold.

In summary, PCS is a complex disorder involving somatic, mood, cognitive and sleep difficulties. The reasons for persistent symptoms vary considerably among children. The TBI is the initial insult, but many pre-existing or environmental factors influence outcome. Early reassurance is a key part of the rehabilitation process and problematic symptoms should be treated promptly, paying particular attention to sleep, headaches and mood disturbance. Most of these problems will respond well to targeted management strategies.

SPINAL CORD INJURY

EPIDEMIOLOGY

The four main causes of acute paraplegia are as follows: trauma (both non-penetrating mechanisms such as diving into shallow water and penetrating injury typically due to gunshot); vascular (including anterior spinal artery syndrome); inflammatory processes (primary infection, and parainfectious processes such as transverse myelitis and acute disseminated encephalomyelitis); and compression caused by tumours, vertebral disc disease, abscesses or syringomyelia. Tumours and other space-occupying lesions may be intrinsic (arising from the cord substance) or more commonly, extrinsic. Compression resulting from expansion of a paraspinal neuroblastoma through a vertebral foramen is an important cause. Syringomyelia (expansion of the central canal) typically causes a slowly evolving deficit, although it may occur suddenly after...
**OUTCOME**

In adult traumatic SCI, complete injury (of both sensory and motor systems) accounts for approximately 50% of cases and is associated with a poorer prognosis and increased mortality. Cervical cord injury is associated with a better functional recovery than thoracic cord injury, although this may be a reflection of an association between thoracic injury and more severe trauma involving cardiopulmonary dysfunction and impaired perfusion of the spinal cord. Some evidence suggests that children may be capable of better neurological recovery from SCI than adults. This may reflect more clear-cut benefits of greater plasticity in the young spinal cord than the immature brain but adult comorbidities such as hypertension and diabetes mellitus probably also impede recovery. However, it is known that very young children tolerate SCI poorly (Schottler et al. 2012). The complications of SCI, including urinary dysfunction, spasticity, pain syndromes, respiratory insufficiency and psychological sequelae, are especially challenging for children and adolescents, and children who suffer injury before their growth spurt are at an increased risk of developing scoliosis.

A large component of the eventual recovery is seen within the first 3 months, although very slight improvement can continue for up to 18 months (Fawcett et al. 2007). As for adults, prognosis for recovery in children is associated with neurological status at presentation, with better recoveries seen in those with incomplete injuries (Sharpe and Forsyth 2013). In the de Goede et al. (2010) study of non-traumatic, non-compressive SCI, complete recovery occurred in >50% of children and fair/poor recovery occurred in >25%. A better prognosis was associated with being aged <10 years, injury at a lumbar spinal level and preceding infection. A worse prognosis was associated with leg flaccidity, urinary incontinence and rapid onset (within 12 hours). In the Sharpe population-based study by Sharpe and Forsyth (2013) of SCI of any cause, 66% made good recoveries with fully or almost independent walking. Bladder involvement at presentation was a poor prognostic sign. Recovery from extrinsic compression is typically good so long as it is promptly recognised and decompressed. Inflammatory lesions usually make reasonable but rarely complete recovery. Vascular injuries (particularly anterior spinal artery syndrome) and severe trauma have the worst prognoses.

**MANAGEMENT ISSUES**

**Emergency Management**

The assessment of a child who has suddenly stopped walking is a neurological–neurosurgical emergency, primarily because of the need to identify and promptly treat spinal cord compression (either medically with steroids or by surgical decompression). The differential diagnosis of this presentation is wide. An important starting point is the distinction of the

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a cough or the Valsalva manoeuvre (e.g. straining at stool), particularly as a secondary complication of other spinal disease. It is thus an important, potentially reversible cause of further spinal cord injury which requires a high index of suspicion and prompt recognition. The earliest clinical sign of expansion of the central canal is isolated involvement of spinohalamic fibres that cross just anterior, resulting in specific loss of pain and temperature sensation at the affected level, which must therefore be specifically tested for if this is a concern. Anterior spinal artery thrombosis is a relatively important cause of apparently spontaneous, acute-onset paraplegia (in the absence of trauma). The anterior spinal artery, running down the ventral (anterior) aspect of the cord, supplies the ventral two-thirds of the cord. As it descends from the vertebral arteries it is supplemented by a variable arrangement of ‘feeder arteries’. Acute infarction reflects this rather precarious blood supply. Onset is typically spontaneous, over minutes and usually has a very poor prognosis (Sharpe and Forsyth 2013). The sparing of the dorsal parts of the cord (which has a separate blood supply) results in the classic clinical picture of paralysis and loss of spinothalamic modality sensation below that level, with preservation of dorsal column sensation.

The annual incidence of spinal cord injury (SCI) in adults is estimated at between ten and 83 per million population with an estimated prevalence of approximately 200–700 per million living with the consequences of SCI at any time (Wyndaele and Wyndaele 2006). Incidence peaks between the ages of 15 and 30 years with a male excess caused by traumatic SCI sustained in road traffic accidents. A second incidence peak in elderly people is the result of falls, tumour compression, spinal stenosis and vascular ischaemia.

Paediatric paraplegia is more rare and less well described in what is a largely aetiology-specific literature. A national cohort study from Taiwan estimated an incidence specifically of traumatic SCI in those aged <18 years of 5.99 per 100,000 person-years (Chien et al. 2012). Again incidence rose markedly in later adolescence, particularly in boys. Road traffic accidents were the most common cause. In a series from a level 1 trauma centre of exclusively traumatic cervical SCI, road traffic accidents were the most common aetiology in young children and sporting injuries in adolescents (Brown et al. 2001).

A prospective population-based surveillance study by de Goede et al. (2010) showed that the annual incidence of transverse myelopathy (of inflammatory or vascular but excluding traumatic aetiologies) in children aged <16 years was 1.71 per million children. There was a bimodal age distribution with incidence greater in under-5s and adolescents. In a population-based survey of paediatric acute paraplegia of all causes, Sharpe and Forsyth (2013) estimated the incidence at 0.49/100,000 children aged <16 per annum. This is a tenth of the incidence reported by Chien et al. (2012) for trauma alone, but the difference may be partially explained by inclusion of 17- and 18-year-olds in the latter study. In the Sharpe study the aetiology was inflammatory in 67%, oncological in 27%, traumatic in 11% and vascular in 9%.
child who genuinely cannot walk (due to weakness) from the child who is reluctant to walk because of pain or anxiety (e.g., fear of falling due to ataxia). This will require persistence and cajoling.

In children who are genuinely and flaccidly weak, the main differentials are acute inflammatory demyelinating neuropathy (AIDP; Guillain–Barré syndrome) and spinal cord dysfunction. In one study, the two most common causes of acute flaccid paralysis were AIDP (47%) and transverse myelitis (19%) (Morris et al. 2003). Pointers to spinal pathology include back pain (compare leg pain, which commonly accompanies AIDP), the presence of injury at a sensory or motor level, urinary symptoms (frequency, dribbling, retention or priapism) and the absence of cranial nerve signs. Children with AIDP are usually totally areflexic, particularly distally. Urgent MRI (ideally of the brain and spine at one sitting, because of the potential for parasagittal lesions to cause a paraplegia) should be performed if there is any clinical possibility of acute spinal pathology. If imaging shows extrinsic compression then emergency paediatric neurosurgical advice should be sought with a demonstration of inflammatory change may reflect vascular or infectious/parainfectious processes. Traumatic injury to the spine can result in remarkably normal cord appearances, an entity known as spinal cord injury without radiological abnormality (SCIWORA).

Medical treatment of cord oedema with high-dose methylprednisolone (e.g., 30mg/kg to a maximum of 1g, followed by infusion of 5mg/kg per hour for up to 18 hours) is widespread. There is some class I evidence to support this in the context of adult traumatic SCI (Bracken 2012). As well as possible decompression, an urgent neurosurgical opinion on the stability of the vertebral column should be sought, particularly in the case of traumatic SCI, and temporary immobilisation (e.g., with ‘halo’ traction or other devices) may be required in the short term.

**Early General Management**

High lesions may require ventilatory support. Children require bladder catheterisation and aggressive management of constipation. Early splinting programmes should be instituted to prevent development of contractures (particularly loss of foot dorsiflexion).

**Autonomic Dysreflexia**

This is an important and characteristic feature of complete SCIs above T6. Noxious stimuli below this level (as trivial as a full bladder or constipation, of which the child has no subjective awareness) lead to increased reflex sympathetic activity in the disconnected lower cord, vasoconstriction and sometimes dangerously severe hypertension. This is sensed by the CNS above the lesion, resulting in increased vagal tone and bradycardia, which can be severe. Above the lesion, vasodilatation results in pounding headache, sweating and red blotches on the skin. Emergency treatment involves the relief of the cause (e.g., catheter blockage) and sitting upright. Extreme care must be taken in administering enemas and other potentially noxious stimuli below the level of the lesion.

**Longer-Term Management**

Many longer-term management issues are shared with children with spina bifida, and these clinics (if available) may be best suited to meet the needs of a child with an acquired paraplegia. Motor morbidity may include weakness, spasticity, and the presence of peripheral contractors. Any effect of these on posture must be aggressively managed, with the use of specialist seating if necessary, to prevent late development of scoliosis particularly in children injured before puberty. Some spasticity of the legs may be helpful in so far as it results in the ability to weight-bear and assist with transfers. However, severe spasticity can result in distressing spasms and intrathecal baclofen pumps can be particularly effective in this group. Skin integrity can be jeopardised by impaired sensation; much as in diabetic neuropathy, pressure sores can result from inadequate nursing care and failure to turn regularly. Likewise, ill-fitting footwear or splints can result in breakdown over pressure areas in anaesthetic skin.

Bowel continence can usually be achieved by use of suppository or enema regimens to effect bowel evacuation at appropriate times. Urinary continence is commonly achieved using clean intermittent catheterisation (which results in a much lower urinary infection rate than permanent urethral catheterisation); however, specialist urological input is required to ensure that the urinary system is ‘safe’, that is, that there is no risk of chronic renal impairment developing as a result of obstructive uropathy.

Psychological support is vital, particularly for young people sustaining an SCI in adolescence. Depression and self-harm are well recognised in adolescents and adults. Sexual function is an important issue in adults.

**REFERENCES**


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Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri

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This chapter begins with an account of the clinical features and management of raised intracranial pressure ([ICP] see also Chapter 7) and cerebral oedema before proceeding to consider brain tumours, other intracranial space-occupying lesions, spinal cord lesions and central nervous system (CNS) complications of leukaemia and lymphomas. It concludes with a discussion of pseudotumour cerebri syndrome (PTSC) also known as idiopathic intracranial hypertension.

**CLINICAL FEATURES AND MIMICS OF INTRACRANIAL HYPERTENSION**

**Early Clinical Features**

Headache is the most common symptom of intracranial hypertension. Although it may be intense and relieved by vomiting, it is more often mild and may be intermittent and/or relieved by commonly used analgesic agents. Headaches may awaken patients at night or be present on arising but these features are only present in a minority of cases. Persistent headache, especially if it occurs in the morning, must always be considered carefully. Morning headaches associate with raised ICP characteristically recur repeatedly and may be associated with lethargy or general malaise. Headaches with these associated symptoms are ‘red flags’ indicating an increased likelihood of an underlying space-occupying lesion (Wilne et al. 2006).

Vomiting is the second most common symptom of raised ICP. It is usually but not always associated with headaches, even in the case of posterior fossa tumours. Vomiting due to raised ICP is usually unremarkable except by its repetition and persistence and by its frequent morning occurrence. Changes in behaviour and personality are commonly an early manifestation of raised ICP. Irritability or lethargy is especially of concern when associated with vomiting and headache. It is important to ask about educational and/or behavioural difficulties as changes may be a feature of intracranial hypertension (Wilne et al. 2007).

Papilloedema (Fig. 14.1) although a major sign is absent in at least half the children with brain tumours, especially supratentorial tumours. The presence of papilloedema makes an intracranial mass highly probable, but its absence in no way excludes such a diagnosis. Papilloedema should be distinguished from pseudo-papilloedema, a congenital anomaly consisting of excessive glial proliferation at the disk margins, and from drusen of the optic nerve head, which, in children, are usually buried within the disk and produce elevation.

**Figure 14.1 Papilloedema** in a child with raised intracranial pressure. Optic nerve head protrudes above level of retina, and limits of disc are obscured by oedema and haemorrhage. (Courtesy of Prof J-L Dufier, Hôpital des Enfants Malades, Paris.)
of the nerve head. In such cases there is no vascular congestion or vessel tortuosity and similar abnormalities are sometimes apparent on fundoscopy of a parent. In difficult cases, ultrasound examination (B scanning) may be useful. Fluorescein fundus angiography is a further investigation that will only rarely be needed. In papilloedema (and not in congenital disc anomalies), it showing a proliferation of the capillary network, exudation of fluorescein out of the vessels and persistence of fluorescence at the disk margins.

Papilloedema is, of course, not specific for brain tumours and can be present with increased ICP of other causes as well as in certain conditions in which ICP is usually not elevated, such as polyradiculoneuritis. Papilloedema should be distinguished from the papilitis of optic neuritis. In the former condition, constriction of the visual fields is classically seen whereas in the latter, blindness or scotoma and eye pain are more common.

Less commonly, raised ICP may present with diplopia due to paralysis of the VIth cranial nerve, which may be unilateral or bilateral and may fluctuate. The specific clinical manifestations of intracranial tumours are considered further in later sections of this chapter.

### Later Clinical Features including those of Brain Herniation

Raised ICP from tumours, hydrocephalus or other causes is dangerous because it leads to reduction of cerebral blood flow, particularly when cerebral perfusion pressure (the difference between mean arterial pressure and ICP) falls to below 40mmHg and its homeostasis fails. Reduced cerebral blood flow can be responsible for lethargy, coma, and a number of autonomic manifestations generally attributed to brain herniation or ‘coning’. Such manifestations may occur only transiently during the ‘plateau waves’ of ICP and disappear with a decrease in intracranial pressure. Relative hypertension and bradycardia (adjusted for the patient’s age) in an awake and seemingly well patient can be features of critically raised ICP. Prompt investigation and treatment is important.

Mass movements of the brain as a result of asymmetrical or unequal expansion of one brain compartment due to the presence of a mass lesion can produce herniation of the cerebral tonsils or brainstem through the foramen magnum or of the uncus hippocampi through the tentorial opening. Both types of herniation may induce secondary brainstem dysfunction, by direct compression against the tentorium or by stretching brainstem vessels. Brainstem dysfunction can occur with global downward movement of the brain substance without lateral herniation. This central syndrome of rostro-caudal deterioration is common with bilateral supratentorial masses. It results in progressive functional impairment, involving in succession the diencephalon, the midbrain and upper pons, the lower pons/upper medulla, and finally the medulla, with eventual death. Brain displacements can be demonstrated by magnetic resonance imaging (MRI) (Johnson et al. 2002), and there is a correlation between the magnitude of displacements and the patient’s level of consciousness. Lateral displacement of the brainstem with uncal herniation is more frequent with unilateral masses. The importance of downward displacements is, however, not clear. Herniation is a late phenomenon and the clinical phenomena attributed to herniation may remain reversible for relatively long periods.

Herniations also produce localised signs, especially compression of the IIIrd cranial nerve by the uncus against the tentorial edge with unilateral pupillary dilatation. Often there is compression of the posterior cerebral artery with occipital infarction. Paralysis of the most caudal pairs of cranial nerves may occur with foramen magnum herniation, which can also be responsible for neck stiffness in children with posterior fossa tumours. Stiffness may be paroxysmal and associated with a rigid extension of the body, the so-called cerebellar fit of Jackson. This is often mistaken for a seizure. A lesser degree of chronic herniation may account for the torticollis that is seen in children with posterior fossa tumours.

Symptoms and signs of very high ICP threatening brain perfusion, including those of herniation, are an indication of imminent danger and require emergency treatment (see below).

### CEREBRAL OEDEMA

#### Definition and Clinical Features

Cerebral oedema is defined as an increase in brain volume due to an increase in its water content. Oedema is an important cause of raised ICP. However, localised oedema need not produce intracranial ICP but may result in focal brain dysfunction.

The diagnosis of brain oedema may be difficult. The clinical manifestations are those of raised ICP and differentiation of brain oedema from cerebral congestion, i.e. increase of cerebral blood volume, may be difficult. Increased blood volume may be caused by epileptic activity, vasoparalysis resulting from asphyxia, head injury, increase in CO₂ content of blood associated with pulmonary or heart disease, venous obstruction, and the effects of drugs such as nitrates, chlornpromazine or halothane.

Cerebral oedema can be detected by imaging. Computed tomography (CT) may show diffuse or localised low attenuation as a result of high water content. On MRI, oedema often presents with intense signal on T2-weighted spin-echo sequences. Diffusion-weighted MRI and diffusion tensor MRI, which allow more precise study of water content and mobility, can give information on the location of oedema in relation to the various cell compartments and be useful for therapeutic orientation (Lu et al. 2004; Sinha et al. 2004). Oedema may be an isolated finding, for example, in patients with diabetic ketoacidosis or following unilateral or focal status epilepticus. It is frequently associated with other entities such as brain tumours and cerebral abscesses.

The symptoms and signs of cerebral oedema are often difficult to separate from those of its causal lesion. The major
consequence of brain oedema is to reduce brain perfusion and produce ischaemia. For this reason the presence of brain oedema, whether in association with other lesions or in isolation, has an important bearing on the understanding and management of the clinical picture.

Types and Causes of Brain Oedema

Cerebral oedema can belong to several types depending on its location and pathogenesis, and each category of oedema is preferentially associated with certain causes.

Vasogenic oedema results from increased permeability of the endothelium of capillaries of the blood–brain barrier, leading to the exudation of protein-rich plasma filtrate into the extracellular fluid. This type of oedema involves most markedly the cerebral white matter in a focal or generalised distribution. Vasogenic oedema is caused by inflammatory processes such as meningitis or abscesses; by brain tumours; by focal lesions that produce an inflammatory response by various mechanisms, such as intracerebral haemorrhages or infarcts; and by disorders that primarily affect the cerebral vessels, such as lead encephalopathy or hypertensive encephalopathy. Oedema that appears in the hours following head trauma probably belongs to this type, as seems also to be the case with focal oedema following partial complex status epilepticus, although, in both cases, more than one cause and one mechanism may be operative. Treatment with corticosteroids is effective only in this type of oedema.

Cytotoxic oedema may coexist with vasogenic oedema. In this type, cellular constituents of the brain, especially astrocytes but also neurons and endothelial cells, undergo rapid swelling as a consequence of dysfunction of the membranes and ionic pumps. The latter is usually due to energy failure and may lead to cellular death, in which case the oedema is irreversible. Hypoxia due to cardiac arrest or to any cause of hypoxic–ischaemic encephalopathy is the most frequent cause, but various toxins and severe infectious processes, and increased ICP itself with decreasing cerebral blood flow, are possible causes. Other mechanisms include neuronal death following status epilepticus and infarction of arterial origin.

Hypo-osmotic oedema is a consequence of osmotic dysequilibrium between a low osmolarity plasma compartment and the higher osmotic pressure of glial cells. Water accumulates within astrocytes. Such occurs with hyponatraemia whether iatrogenic or due to inappropriate antidiuretic hormone (ADH) secretion, in patients with diabetes mellitus during treatment of ketoacidosis, and with the dysequilibrium syndrome of patients undergoing dialysis for renal failure or other reasons.

Interstitial oedema is caused by the transepidermal resorption of cerebrospinal fluid (CSF) from the ventricles into the extracellular space in patients with hydrocephalus. This type of oedema is clearly shown by CT or MRI, which demonstrate areas of decreased attenuation in a periventricular distribution, especially around the anterior and posterior horns of the ventricles.

Table 14.1 Symptoms and signs of decompensation with raised intracranial pressure

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness (use modified coma scale)</td>
<td>Downward displacement of the ponto-thalamic junction* (&lt;span style='color:red'&gt;Reich et al. 1993&lt;/span&gt;; &lt;span style='color:red'&gt;Ropper 1993&lt;/span&gt;)</td>
</tr>
<tr>
<td>Uni/bilateral hypertonia</td>
<td>Lateral displacement of the brainstem (&lt;span style='color:red'&gt;Ropper 1989&lt;/span&gt;)</td>
</tr>
<tr>
<td>Decoricate posturing</td>
<td>Tonsillar herniation</td>
</tr>
<tr>
<td>Decerebrate posturing</td>
<td></td>
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<tr>
<td>Uni/bilateral extensor plantar sign</td>
<td></td>
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<tr>
<td>Unilateral IIIrd nerve palsy</td>
<td></td>
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<tr>
<td>Pupillary dilatation, unilateral or only sluggishly reacting to light</td>
<td></td>
</tr>
<tr>
<td>Unilateral VIth nerve palsy</td>
<td></td>
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<tr>
<td>Paralysis of upward gaze</td>
<td></td>
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<tr>
<td>Yawning, periodic respiration, spontaneous hyperventilation, shallow or irregular respiration</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
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</tbody>
</table>

*Downward or lateral displacements of the brainstem are generally well correlated with clinical symptoms and signs. They are indication of impending risk even when clinical signs are absent.

Hydrostatic oedema results when increased intravascular pressure is transmitted to the capillary bed because of a lack of compensatory increase in the vascular resistance, with resulting outpouring of water into the extracellular space. Such an event occurs when the complex mechanisms of brain vascular autoregulation fail.

Intramyelinic oedema is less common. It has been observed mainly following intoxication, for example, with triethyltin and hexachlorophene. The oedema is located between myelin lamellae forming intramyelinic ‘bubbles’. This type of oedema is always diffuse in distribution, involves mainly the white matter, and may affect the spinal cord.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

Raised ICP is a major problem in patients with brain tumours and other expansive lesions, and also in several acute pathological situations such as trauma, brain infections or ischaemia. It is responsible for many complications including mass displacements of the brain and herniation, so its early recognition and treatment are essential. The symptoms and signs that herald impending life-threatening complications are listed in Table 14.1. These are usually attributed to herniation, but high ICP with resulting decrease in cerebral blood flow
ICP can be determined in various ways but a single measure of pressure can often be obtained. The goal of treatment is to reduce ICP to keep cerebral perfusion pressure above 50mmHg to ensure adequate oxygenation of the brain. Since cerebral perfusion pressure equals the difference between mean arterial pressure and ICP, the maintenance of systemic blood pressure is crucially important. ICP can be determined in various ways but a single measure is of little value to guide management. For this reason, continuous ICP monitoring has gained increasing acceptance. It should be stressed, however, that it is certainly more important to treat urgently any underlying cause, such as meningitis, than to insert an ICP monitor. Reversal of flow throughout the diastole on Doppler study is usually seen when cerebral perfusion pressure approaches zero, while EEG slowing and low amplitude are correlated with poor perfusion of the brain.

The treatment of raised ICP, irrespective of its cause, includes meticulous avoidance of all factors, such as painful stimuli, which may transiently increase ICP. Crystalloid fluids should be restricted to approximately 60–70% of the age-appropriate requirements, and hypo-osmolar fluids avoided. An adequate circulation must be quickly restored, if necessary with volume expanders and vasopressor agents such as dopamine (10–20µg/kg/min) and then maintained with lower doses (2µg/kg/min) as required. Control of seizures, which increase secondary deterioration, should be vigorously pursued.

It is probably reasonable to administer mannitol (0.25–2mg/kg in 20% solution) as a bolus over 10–15 minutes as an emergency measure temporarily to relieve a spike of raised ICP while other, more sustainable, interventions are initiated. Higher doses have been advised by some (Cruz et al. 2004). Its peak action occurs within 30 minutes and its effect may last from 2 to 6 hours but prolonged use may be associated with rebound intracranial hypertension and aggravation of vasogenic oedema. The use of occasional small (0.25mg/kg) doses in response to acute rises of ICP therefore tends to be preferred to regular doses without ICP monitoring.

Hyperventilation produces cerebral vasoconstriction and decreases cerebral blood volume at least initially. The effect of prolonged hyperventilation is controversial as the vasoconstrictive effect may disappear; haemodynamic responses in the unconscious patient are often altered so that a decrease of CO₂ may be associated with rebound intracranial hypertension and aggravation of vasogenic oedema. The use of occasional small (0.25mg/kg) doses in response to acute rises of ICP therefore tends to be preferred to regular doses without ICP monitoring.

Steroids are mainly useful for treatment of the perifocal oedema of tumours or abscesses. Dexamethasone is commonly used. The drug is generally given intravenously at a dose of 0.1–0.25mg/kg body weight initially and may be continued parenterally or orally in a total dose of 0.25–0.5mg/kg/day in four divided doses (Han and Sun 2002). High-dose pulses may be more effective.

Barbiturate coma is not indicated, except perhaps in intractable cranial hypertension and in raised ICP due to status epilepticus. The alleged protective effect of barbiturates on the brain has not been confirmed. Thiopentone is often used in doses of 3–5mg/kg over 10–20 minutes, followed by infusions of 1–2mg/kg at intervals of 1 or 2 hours. This agent seriously interferes with EEG monitoring of cerebral function.

Hypothermia is still used by some clinicians but its role is disputed. External diversion of CSF may be useful for certain neurosurgical patients. Surgical decompression is an exceptional life-saving measure the indications for which are very few.

### Table 14.2 Main causes of non-traumatic increased intracranial pressure (excluding intracranial mass lesions and hydrocephalus)

<table>
<thead>
<tr>
<th>Cause</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary intracranial diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Chapter 11</td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
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<tr>
<td>Encephalitis</td>
<td></td>
</tr>
<tr>
<td>Reye syndrome</td>
<td></td>
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<tr>
<td><strong>Cerebrovascular diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Bleeding secondary to vascular</td>
<td>Chapter 15</td>
</tr>
<tr>
<td>malformations</td>
<td></td>
</tr>
<tr>
<td>Arterial strokes</td>
<td>Mori et al. (2001)</td>
</tr>
<tr>
<td>Sinus and venous thrombosis</td>
<td>Sèbire et al. (2005)</td>
</tr>
<tr>
<td><strong>Systemic diseases with cerebral involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis and coma</td>
<td>Chapter 22</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>Chapter 14</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
</tr>
<tr>
<td>Cystinosis</td>
<td>Dogulu et al. (2004)</td>
</tr>
<tr>
<td>Haemolytic–uraemic syndrome</td>
<td>Chapter 22</td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td></td>
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<tr>
<td>Hepatic encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Hypoxic–ischaemic encephalopathy</td>
<td>Chapters 12, 14</td>
</tr>
<tr>
<td>of any cause</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Henry et al. (2004)</td>
</tr>
<tr>
<td><strong>Toxic/traumatic causes</strong></td>
<td></td>
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<tr>
<td>Head trauma</td>
<td>Chapter 13</td>
</tr>
<tr>
<td>Near-drowning</td>
<td></td>
</tr>
<tr>
<td>Lead toxicity</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine, tacrolimus</td>
<td>Lewis (1999), Kwon et al. (2001)</td>
</tr>
</tbody>
</table>
Chapter 14  Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri

BRAIN AND OTHER INTRACRANIAL TUMOURS

FREQUENCY AND AETIOLOGICAL FACTORS OF CNS TUMOURS

Tumours of the CNS are the second most common malignancy of childhood after leukaemia, accounting for 20% of all childhood malignancies. The overall population incidence of intracranial neoplasms varies between one and three per 100,000 in different series (see Baldwin and Preston-Martin 2004). However, the incidence rises to 5.42 per 100,000 for children and adolescents aged 0–19 years of age when benign tumours are included (Ostrom et al. 2014). Approximately 10% of tumours occur in children under 2 years of age, 20% between 2 and 5 years, 25% between 3 and 10 years, and 45% between 10 and 19 years. Overall, supratentorial tumours account for about half the cases (Ostrom et al. 2014) (Fig. 14.2a, b), but their location varies with age. In infants, there is a predominance of supratentorial tumours (especially astrocytomas) over infratentorial neoplasms, (mainly medulloblastomas and ependymomas). In children older than 4 years, infratentorial tumours (mostly cerebellar astrocytomas, medulloblastomas and ependymomas) are the most frequent.

Low grade gliomas represent 40% of all childhood brain tumours and are the commonest solid tumour of childhood requiring active management. Most are sporadic, arising within a single location including hypothalamus, chiasm, optic nerves, cerebellum, cerebral cortex, brainstem and spinal cord, with metastatic dissemination in fewer than 10%. Up to 15% are associated with neurofibromatosis type 1 (NF1). Hypothalamic chiasmatic low grade gliomas most commonly present in the first 2 years of life, the younger the patient, the larger the tumour. Low grade gliomas may occur at any age in childhood in the cerebellum but tend to occur in later childhood in the cerebral cortex, brainstem and spinal cord and this is also true for NF1-associated tumours (Guillamo et al. 2003).

The reasons for the changing age distribution of supratentorial and infratentorial tumours, for the predominance of midline tumours in children compared to adults, the predominance of ventricular tumours and for the predominance of neuro-ectodermal neoplasms in childhood are poorly understood (Bunin 2004). It is becoming increasingly clear that specific genetic mutations in each of the tumour types are associated with anatomical locations as well as the specific tumour type. This regional determination of genetic mutation underlies the anatomical determinant of embryological development that is presumably disordered in tumours that develop within specific regions of the brain during early life (Gibson et al. 2010; Jones et al. 2013; Pajtler et al. 2015).

Genetic Factors

Understanding of the genetics of brain tumours has evolved rapidly over the last 20 years and this is reflected in the appearance for the first time of genetic criteria alongside histological criteria in the classification of tumours of the CNS published by the World Health Organization (WHO) in 2016 (Louis et al. 2016).

From the cytogenetic point of view, the development of cancer is a multistep process in which some cells acquire a series of genetic insults that disrupt their normal development and fate as a result of dysfunction of oncogenes, tumour suppressor genes and stability genes (Vogelstein and Kinzler 2004; Gilbertson 2005). It has long been known that the cells of many tumours contain acquired chromosomal abnormalities that result apparently from new mutations (e.g. deletions of certain chromosomes or part thereof) as they do not exist in the cells of other organs. Such chromosomal abnormalities (e.g. abnormalities of chromosome 22 in acoustic schwannomas) are frequently present in other tumour cells; for example, deletions of 10q, 11 and 17p in medulloblastoma, and deletions of 1p and 19q in certain oligodendrogliomas. Interestingly, these anomalies may differ among different cases of the same tumour type and these differences have a prognostic significance; for example, the presence of the p53 gene (Sung et al. 2000; Pollack et al. 2001) or the amplification of the MYC gene in neuroblastoma.

Molecular genetic studies (Gilbertson 2005) that resulted from the discovery of these chromosomal aberrations have led to breakthroughs in the understanding of the biology of tumours. Some genes have the property of opposing or slowing down their development (tumour suppressor genes or anti-oncogenes), some stabilise signalling pathways, while others favour their growth (oncogenes) or predispose to certain types of cancer.

The mechanisms are illustrated by the case of the retinoblastoma, a retinal neoplasm that usually develops in young children below 4 years of age and often metastasises to the CNS. Retinoblastoma is familial in 40% of cases because of a heritable predisposition to this tumour and others (e.g. osteosarcoma) and sporadic in the remaining 60%. Hereditary predisposition is determined by mutations at a locus within the q14 band of chromosome 13 and sporadic cases have somatic mutations at the same genetic locus. The gene for sensitivity to retinoblastoma normally functions as a dominant suppressor of tumour formation and this function has to be lost in both homologous alleles for a retinoblastoma to develop. In persons who have inherited a genetic mutation, a second, somatic mutation is sufficient to lead to clinical disease (‘two-hit’ hypothesis), whereas two somatic mutations are required for non-genetic cases, a much less likely event.

The genetic characterisation of childhood brain tumour types has been the focus of intensive recent remarkable collaborations by research consortia that share samples and investigative strategies. Examples of the resulting practical consequences are described in the sections that follow relating to particular tumour types and include major revisions of
Figure 14.2a  Distribution in children and adolescents (ages 0–19) of primary brain and central nervous system tumours by site \((n=22,535)\), Central Brain Tumor Registry of the United States Statistical Report: National Program of Cancer Registries and Surveillance, Epidemiology and End Results, 2007–2011 (Ostrom et al. 2014).

the understanding of of medulloblastomas, other embryonal tumours, ependymomas, pilocytic astrocytomas and diffuse gliomas. This molecular re-classification will drive future trials of therapy and an increasingly ‘ personalised’ approach to therapy by identifying more reliably ‘good players’ requiring less intensive approaches and identifying ‘bad players’ where novel targeted approaches are justified.

Genetic Syndromes Predisposing to Tumours of the CNS

Most tumours of the CNS occur in children without predisposing factors. However, there are a group of syndromes that predispose children to intracranial neoplasms which can be considered either as associations of specific tumour types with underlying genetic syndromes (Table 14.3a) or as associations of genetic syndrome with specific tumour types (Table 14.3b).

The list of these associations continues to expand and become increasingly specific. In some genetically transmitted immunodeficiency syndromes; for example, Wiskott–Aldrich syndrome and ataxia–telangiectasia, the incidence of tumours is also high.

Environmental Factors

The backdrop of brain developmental growth parameters and genetic factors sets the scene for interaction with environmental stimuli that may trigger tumour development. It is clear now that it is difficult to study these factors in isolation from each other. A recent meta-analysis of environmental aetiology for CNS tumours (Walker et al. 2016) has identified the factors for which there is most evidence.

Acquired immune deficiency syndrome (AIDS) complicating infection with human immunodeficiency virus (HIV) is associated with primary non-Hodgkin lymphoma (NHL) of the CNS in around 0.5% of patients with AIDS and 50% of NHL of the CNS is associated with HIV. This risk is reducing in size in North America, Europe and Australia with the introduction of highly active anti-retroviral therapy (International Collaboration on HIV and Cancer 2000).

Ionising Radiation

Ionising radiation is an established environmental risk factor for CNS tumours. Cranial and spinal radiotherapy for cancer, including prophylactic CNS irradiation as part of the treatment for childhood leukaemia, increases the risk of CNS tumours in young people. The predominant tumour types are meningiomas and high-grade astrocytomas. There is also supporting evidence for radiation related to diagnostic imaging including CT for brain tumour. Evidence for a tumorigenic effect of high background radiation is not strong.

Non-ionising Radiation

There is less evidence that exposure to non-ionising radiation such as electromagnetic fields is a risk factor for brain tumours. The absence of a dose–response relationship in most studies makes the results hard to interpret. Epidemiological studies of exposure to radiofrequency emissions from use of mobile telephones suggest that the existence of a substantial risk over a short time of use is unlikely but that there is insufficient evidence regarding the possibility of a small increase in risk or a risk related to longer periods of exposure.

Carcinogens

Intra-CSF (intrathecal) methotrexate with a cumulative exposure more than 70mg/m² is associated with an increased risk of meningioma with a relative risk of 35.6 after adjustment for exposure to radiation (Taylor et al. 2010). N-nitroso compounds (NOCs) are contained in cured meat and tobacco smoke and are known potent carcinogens. Estimation of their effect on the risk of developing a brain tumour is based upon largely unvalidated data for cured meats. There is little evidence of an association between parental smoking, alcohol intake, coffee or tea drinking and CNS tumorigenesis. There is some evidence that parental exposure to pesticides is a risk factor for childhood CNS tumours, but there has been little consistency in studies of other parental occupations (Van Maele-Fabry et al. 2013; Chen et al. 2015).

Birthweight and Fetal Growth Rate

There is some evidence that increased birthweight is associated with enhanced risk for all brain tumours and pilocytic astrocytoma in particular.

Epilepsy and Head Injury

Increased risk of glioma in association with a history of epilepsy has been found in several studies of children and adults. It seems likely, however, that this reflects, at least in part, the fact that epilepsy can be an early symptom of a brain tumour, especially low grade astrocytomas of childhood.

Protective Effects

Many studies have found a protective effect of prenatal vitamin or folic acid supplements against childhood brain tumours. There is a growing body of evidence that past history of allergies, asthma or eczema or certain common viral infections are protective against glioma and meningioma, suggesting immunological mechanisms. The apparent protective effect of female reproductive hormones is consistent with the generally lower incidence of glioma in women compared with men. High levels of physical activity and the presence of diabetes have been found to be protective.

Clinical Manifestations and Diagnosis

Children with brain tumours present with symptoms of increased ICP (considered above), focal neurological deficits or epilepsy. Presentation with symptoms in the absence of
### Table 14.3a  Inherited predisposition to brain tumours: Tumour types by underlying genetic syndromes

<table>
<thead>
<tr>
<th>Central nervous system tumour type</th>
<th>Associated gene syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROEPITHELIAL TUMOURS</strong></td>
<td></td>
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<tr>
<td>Astrocytic tumours</td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Constitutional mismatch repair deficiency syndrome (MSH2, MSH6, MLH1, PMS2)</td>
</tr>
<tr>
<td></td>
<td>Familial adenomatous polyposis (APC)</td>
</tr>
<tr>
<td></td>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 1 (NF1)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 2 (NF2)</td>
</tr>
<tr>
<td></td>
<td>Nevoid basal cell carcinoma syndrome (PTCH/SUFU)</td>
</tr>
<tr>
<td></td>
<td>Tuberous sclerosis complex (TSC)</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Tuberous sclerosis complex (TSC)</td>
</tr>
<tr>
<td>Pilocytic astrocytoma/optic pathway tumours</td>
<td>Neurofibromatosis type 1 (NF1)</td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 1 (NF1)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Constitutional mismatch repair deficiency syndrome (MSH2, MSH6 MLH1, PMS2)</td>
</tr>
<tr>
<td></td>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 1 (NF1)</td>
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<tr>
<td>Ependymal tumours</td>
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<tr>
<td>Ependymoma</td>
<td>Familial adenomatous polyposis (APC)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 2 (NF2)</td>
</tr>
<tr>
<td>Choroid plexus tumours</td>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td>Neuronal and mixed glioneuronal tumours</td>
<td>Cowden syndrome (PTEN)</td>
</tr>
<tr>
<td>Dysplastic gangliocytoma of cerebellum</td>
<td>Pallister–Hall syndrome (GLI3)</td>
</tr>
<tr>
<td>Hypothalamic hamartoma</td>
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<tr>
<td>Tumours of the pineal region</td>
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<tr>
<td>Pineoblastoma</td>
<td>DICER1 syndrome (DICER1)</td>
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<td>Hereditary retinoblastoma (RB1)</td>
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<td>Embryonal tumours</td>
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<tr>
<td>Medulloblastoma</td>
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<td>Familial adenomatous polyposis (APC)</td>
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<td>Li–Fraumeni syndrome (TP53)</td>
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<td></td>
<td>Ataxia–Telangiectasia (ATM)</td>
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<td>Constitutional mismatch repair deficiency syndrome (MSH2, MSH6 MLH1, PMS2)</td>
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<tr>
<td></td>
<td>Fanconi anaemia (FANCD1/BRCA2, FANCN or PALB2)</td>
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<tr>
<td></td>
<td>Rubinstein Taybi syndrome (CREBBP)</td>
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<tr>
<td>Embryonal tumour with multilayered rosettes</td>
<td>DICER1 syndrome (specifically medulloepithelioma)</td>
</tr>
<tr>
<td></td>
<td>Constitutional mismatch repair deficiency syndrome (MSH2, MSH6 MLH1, PMS2)</td>
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<tr>
<td></td>
<td>Fanconi anaemia (FANCD1/BRCA2, FANCN or PALB2)</td>
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<td></td>
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</tr>
<tr>
<td>Atypical teratoid/rhabdoid tumour</td>
<td>Rhabdoid tumour predisposition syndrome, type 1 (SMARCB1)</td>
</tr>
<tr>
<td></td>
<td>Rhabdoid tumour predisposition syndrome, type 2 (SMARCA4)</td>
</tr>
<tr>
<td>Pituitary blastoma</td>
<td>DICER1 syndrome (DICER1)</td>
</tr>
<tr>
<td><strong>TUMOURS OF CRANIAL AND PARASPINAL NERVES</strong></td>
<td></td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Carney complex (PRKAR1A)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis Type 2 (NF2)</td>
</tr>
<tr>
<td></td>
<td>Schwannomatosis (SMARCB1)</td>
</tr>
<tr>
<td>Vestibular schwannoma</td>
<td>Neurofibromatosis Type 2 (NF2)</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>Neurofibromatosis Type 1 (NF1)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis Type 2 (NF2)</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>Neurofibromatosis type 1 (NF1)</td>
</tr>
<tr>
<td></td>
<td>SMARCB1 mutations</td>
</tr>
</tbody>
</table>

*Continued*
any abnormal clinical signs on examination is rare except in the case of seizures. Two or more unexplained seizures with focal clinical or electrographic features are, for this reason, a clear indication for cranial imaging in all children. The symptoms and signs differ with the location of the tumour and, to a lesser extent, its histological nature (e.g. depending on the importance of the oedema). The initial clinical symptomatology of intracranial tumours is, however, often nonspecific and may include minor clinical symptoms that may not be different from those in common benign illnesses of children. The occurrence of several such symptoms in combination with each other should raise the clinician’s index of suspicion of a CNS tumour and lower the threshold for cranial imaging correspondingly. The possibility of a CNS neoplasm should always be kept in mind, especially if there is persistence or progression of symptoms, even if the diagnosis only rarely proves to be correct.

A consecutive series of 200 cases of childhood intracranial tumours seen over a 14-year period reported on the relative incidence and duration of symptoms and signs (Wilne et al. 2006). With respect to symptoms, headache was the first reported symptom in around 40% and was the commonest symptom overall, reported by over half of children prior to diagnosis. Vomiting, educational and/or behavioural difficulties each occurred in around 40% of cases at some point and each occurred as the first symptom in around 10% of cases. Seizures occurred at some point in 15% and as the first symptom in around 10% of all cases. With respect to clinical signs, a high rate of abnormalities on examination was evident in the above series with respect to cranial nerve abnormalities (49%), cerebellar signs (48%) and papilloedema while long tract signs were less common (27%). A cranial nerve abnormality and/or papilloedema were the only abnormalities on clinical examination in 20%. Excessive head growth or endocrine problems, including growth failure and/or an abnormal trajectory of weight gain, were less common features although macrocephaly was a common feature in infants. Lower rates of both clinical symptoms and clinical signs were found in a subsequent meta-analysis of 74 reports of clinical features (Wilne et al. 2007) (Fig. 14.3).

In the 2006 report by Wilne et al., the median symptom interval before diagnosis was 2.5 months. The range of symptom intervals was 0–120 months with the longest intervals seen with seizures or endocrine features and a shorter than average symptom interval significantly associated with high-grade tumours and patient age of 3 years or younger. A subsequent similar study of 139 children presenting to four UK centres in 2004–2006 reported a median duration of symptoms prior to diagnosis of 3.3 months and found that longer symptom interval was associated with head tilt, cranial nerve palsies, endocrine and growth abnormalities and reduced visual acuity. More than half of children with brain tumours developed problems, between symptom onset and diagnosis, with vision and more than a third developed motor problems, cranial nerve palsies, behavioural change or nausea and vomiting. Lethargy, weight problems and other features suggesting endocrine dysfunction were highlighted as features whose clinical significance was under-recognised (Wilne et al. 2012).

The UK HeadSmart Be Brain Tumour Aware Campaign (www.headsmart.org), launched in 2011, targeted the medical profession and the public with graded health messages including specific advice on referral versus observation. In this project the tumour groups with the longest total diagnostic intervals were midline supratentorial craniopharyngiomas and intracranial germ cell tumours, presenting with endocrine and visual symptoms and signs, and low grade gliomas presenting with progressive and slowly evolving symptomatology. Twenty per cent of the population indicated some awareness of the project and a significant reduction in total diagnostic interval over a 9-year period coincided in time with the project, suggesting that health systems can be influenced by providing specific guidelines for a rare condition.

**Non-focal features of raised intracranial pressure as manifestations of intracranial tumours**

These are detailed in the opening paragraphs of this chapter.
Focal features of intracranial tumours

Focal neurological features of brain tumours depend mainly on the location of the tumour. The value of careful examination of the cranial nerves, including fundoscopy, is under-recognised. In practice an eye check by an optician is a relatively frequent route of referral for a scan. However, some focal signs are of no localising value in the presence of intracranial hypertension. This applies particularly to paralysis.

<table>
<thead>
<tr>
<th>Table 14.3b Inherited predisposition to brain tumours: Genetic syndromes by associated tumour types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome (gene)</td>
</tr>
<tr>
<td>Ataxia–telangiectasia (ATM)</td>
</tr>
<tr>
<td>Constitutional mismatch repair deficiency syndrome (MSH2, MSH6 MLH1, PMS2)</td>
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<tr>
<td>Familial adenomatous polyposis (APC)</td>
</tr>
<tr>
<td>Carney complex (PRKARIA)</td>
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<tr>
<td>Cowden syndrome (PTEN)</td>
</tr>
<tr>
<td>DICER1 syndrome (DICER1)</td>
</tr>
<tr>
<td>Fanconi anaemia (FANCD1/BRCA2, FANC-N or PALB2)</td>
</tr>
<tr>
<td>Hereditary retinoblastoma (RBI)</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome (TP53)</td>
</tr>
<tr>
<td>Neurofibromatosis type 1 (NF1)</td>
</tr>
<tr>
<td>Neurofibromatosis type 2 (NF2)</td>
</tr>
<tr>
<td>Nevoid basal cell carcinoma syndrome (PTCH/SUFU)</td>
</tr>
<tr>
<td>Rhabdoid tumour predisposition syndrome (SMARCB1)</td>
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<tr>
<td>Rubinstein Taybi syndrome (CREBBP)</td>
</tr>
<tr>
<td>Schwannomatosis (SMARCB1)</td>
</tr>
<tr>
<td>Tuberous sclerosis complex (TSC)</td>
</tr>
<tr>
<td>Von Hippel–Lindau (VHL)</td>
</tr>
</tbody>
</table>

*Previously known as primitive neuro-ectodermal tumour.

The list of these associations continues to expand and become increasingly specific. In some genetically transmitted immunodeficiency syndromes, e.g. Wiskott–Aldrich syndrome and ataxia–telangiectasia, the incidence of tumours is also high.
and dysequilibrium is prominent. There is often no nystagmus, dysmetria or adiadochokinesis, the tumour may be observed.

Paradoxical mydriasis of the pupil contralateral to the side of the oculomotor nerve. In general, compression of the oculomotor nerve by a herniated uncus produces only involvement of the pupillary fibres with unresponsive mydriasis whereas cranial nerve palsies of the VIth nerve arise as a consequence of compression of the nerve fibres stretched over angular bony structures. Rarely, paralysis of the abducens nerve and less commonly to paralysis of the oculomotor nerve.

Clinical and Radiological Diagnosis and Other Investigations

The current diagnostic approach to a suspected brain tumour is based primarily on neuroimaging. A quick reference guide regarding the clinical features of brain tumours in children in three age bands that can be used to assist in the decision to undertake cranial imaging is available at https://www.rcpch.ac.uk/search/apachesolr_search/Diagnosing%20Brain%20Tumours%20in%20Children.

MRI is usually the investigation of choice. It provides better anatomical resolution than CT, except for visualisation of intracranial calcification, and is superior to CT for diagnosis and surgical planning in most brain tumours. It is particularly useful in imaging the posterior fossa, small lesions located close to bony structures and for detection of meningeal dissemination. MRI of the brain and spine, pre- and post-contrast, particularly with fluid attenuation inversion recovery (FLAIR) and diffusion-weighted imaging sequences, is now becoming an essential tool for assessment of childhood brain tumours and of sequelae related to their treatment (Chang et al. 2003; Warren 2005).

With the advent of CT, plain X-rays of the skull were largely superseded in the investigation of a patient with a suspected brain tumour except in resource poor settings. Radiological features of brain tumours on skull X-rays include widening of sutures, abnormal digital markings, and rarefaction of the posterior clinoids and lamina dura in the
pituitary fossa. Calcification may be seen in certain tumour types particularly craniopharyngioma. CT has, in its turn, been partly superseded by MRI in the diagnosis of intracranial tumours although it remains the mainstay of emergency and out of hours investigation in many centres. CT is an excellent imaging modality for identification of intracranial calcification (Renowden 2005). It is also fast so young children may avoid the requirement for a general anaesthetic for scanning purposes, and cheaper than MRI, but requires exposure to radiation and this may have long-term implications such as secondary tumours (Mathews et al. 2013).

If only CT is available, it should be performed with and without injection of iodine contrast substance except in patients with allergy to iodine. Unenhanced scans may rarely fail to reveal existing tumours, and the presence and degree of enhancement provides information on the nature of the tumour. Functional imaging is less precise from a morphological point of view but may have specific indications; for example, to localise essential functional areas that must be respected.

Magnetic resonance spectroscopy (MRS) is performed in many centres. It may allow chemical characterisation of paediatric brain tumours (Carless et al. 2002a; Tzika et al. 2002; Tzika et al. 2004). Positron emission tomography (PET), combined with CT or MRI, together provide both precise anatomical information and functional metabolic assessment of malignant tumours. The sensitivity of 18F-fluorodeoxyglucose (FDG) is limited by the high rate of glucose metabolism of healthy brain tissue and more recent studies with PET in brain tumours have investigated the use of radiotracers other than FDG. 18F-fluoroethyl choline (FEC) has, for example, been shown to be an effective metabolically stable radiotracer for imaging cellular metabolism in astrocytic and non-germinomatous germ cell tumours (Treglia et al. 2012; Fraioli et al. 2015; Tsouana et al. 2015) (Fig. 14.4).

Examination of the CSF is usually not essential for the diagnosis. In specific instances the CSF may be indicated for cytology, especially for the detection of meningeal spread, and in cases of leukaemia, malignant meningeal tumours or melanomas. The presence of malignant cells in the CSF is not uncommon with malignant tumours such as medulloblastomas or ependymomas. Although false positives are rare, false negative results are fairly common. A search for CSF biochemical markers (e.g. human chorionic gonadotropin or alphafetoprotein) is useful in germ cell tumours.

In most cases where there is evidence of raised ICP the dangers of lumbar puncture probably outweigh the information provided. How often a lumbar puncture produces or hastens the occurrence of transtentorial herniation is difficult to determine and the literature presents conflicting opinions in this regard. If in doubt, it is safer to refrain from performing lumbar puncture. For example if there is an intracranial tumour and a contraindication to lumbar puncture (Kneen et al. 2012) (see Table 14.4) but also clinical suspicion of CNS infection, it is usually possible to initiate empirical treatment for possible meningitis without undertaking lumbar puncture.

Figure 14.4 18F-fluoroethyl choline positron emission tomography/magnetic resonance imaging in adolescents with intracranial nongerminomatous germ cell tumours. Reproduced from Tsouana et al. Evaluation of treatment response using integrated 18Flabeled choline positron emission tomography/magnetic resonance imaging in adolescents with intracranial nongerminomatous germ cell tumours. Reproduced from Tsouana et al. Evaluation of treatment response using integrated 18Flabeled choline positron emission tomography/magnetic resonance imaging in adolescents with intracranial nongerminomatous germ cell tumours. Pediatric Blood and Cancer, Vol 6: 1661-3 © 2015 with permission from John Wiley and Sons.

Any decision to proceed with lumbar puncture (or not) will need to take clinical features that might indicate raised ICP into account, whether or not recent cranial imaging is available. In a child who is either sedated or has had clinical signs that are suggestive (but not confirmatory) of raised ICP, this decision should only be made by a clinician experienced in the neurological/neurosurgical aspects of care of children with neurological problems. The advent of CT and MRI has considerably simplified this problem, and CT/MRI should be obtained before lumbar puncture when there is a suspicion of a mass lesion although a ‘normal’ scan does not exclude raised ICP.

The differential diagnosis of brain tumours includes other intracranial mass lesions, hydrocephalus, intracranial haemorrhages and infections and pseudotumour cerebri syndrome (also known as idiopathic intracranial hypertension). The last of these is considered at the end of this chapter.

CNS TUMOUR BIOLOGY, PATHOLOGY, STAGING AND THEIR RELATION TO MANAGEMENT

The World Health Organization 2016 Classification of Central Nervous System Tumours

The 2007 classification of CNS tumours was replaced by WHO CNS 2016 whose authors stated that a further revision is likely to be required less than nine years thereafter. This classification uses, for the first time, molecular parameters
The presenting brain injury and so represents a significant risk to the patient. Pathological diagnosis and grading is only one element of interdisciplinary discussion that also needs to consider associated genetic predisposition, age, brain region, precise location, staging and, in some cases, change over time on serial neuroimaging to determine what the likely implications of a tumour are, for a particular patient.

Tumours of the CNS are assigned grades of malignancy based primarily on histological morphology. The WHO has a I–IV grading of least malignant to highly malignant with a specific grade assigned to each tumour entity rather than multiple grades within an entity. The 2016 WHO CNS classification has broken with this tradition in the case of an entity that they now describe as ‘solitary fibrous tumour/haemangiopericytoma’ (Louis et al. 2016). Tumours in this entity are placed in a single group because they share a number of molecular abnormalities but within the group these may be graded I, II or III on the basis of histological features (e.g. number of mitoses per high powered field). This is a further example of the way that molecular characterisation is altering the way that CNS tumours are classified.

CNS tumours are also assigned a stage from I to IV corresponding to localised disease, evidence of malignant cells in the CSF, solid metastasis and widespread metastases respectively. Note that even malignant CNS tumours rarely metastasise outside the CNS; most CNS tumours tend to metastasise along CSF rather than haematogenous pathways (Curless et al. 2002b).

### TREATMENT OF BRAIN TUMOURS

#### General Considerations

The survival rates among children with brain tumours vary with their nature and location. The worst prognosis is for children with diffuse midline tumours predominantly arising in the brainstem (now referred to as diffuse midline glioma H3 K27M mutant) whereas almost 100% of children with cerebellar astrocytoma, and 70–90% of those with low grade hemispheric astrocytoma are alive at 5 years from diagnosis. Children under 2 years of age with tumours have a lower survival rate than older children (see below) and their quality of life is often poor.

Surgery is generally the primary treatment for paediatric brain tumours. Complete macroscopic resection of brain tumours is always the aim of surgery as it is associated with the best results in terms of survival and disease free survival particularly in paediatric tumours. However, this cannot be accomplished in many cases as the associated morbidity/mortality would be unacceptable. In these situations partial resection may be useful to reduce the bulk of the tumour followed by adjuvant treatment in the form of radiation therapy and/or chemotherapy (Estlin 2005). Stereotactic neurosurgery has considerably developed for accurate biopsy of deep seated brain tumours. The use of neuro-navigation has transformed the surgical management of brain tumours in terms of accurate localisation of the craniotomy and the tumour. It is now

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Table 14.4 Contraindications to lumbar puncture

<table>
<thead>
<tr>
<th>Imaging needed before lumbar puncture (to exclude brain shift, swelling or space-occupying lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe impairment of consciousness (GCS &lt;13)” or fall in GCS of &gt;2</td>
</tr>
<tr>
<td>Focal neurological signs (including unequal, dilated or poorly responsive pupils)</td>
</tr>
<tr>
<td>Abnormal posture or posturing</td>
</tr>
<tr>
<td>Papilloedema</td>
</tr>
<tr>
<td>After seizures until stabilised</td>
</tr>
<tr>
<td>Relative bradycardia with hypertension</td>
</tr>
<tr>
<td>Abnormal ‘doll’s eye’ movements</td>
</tr>
<tr>
<td>Immunocompromise</td>
</tr>
<tr>
<td>Other contraindications</td>
</tr>
<tr>
<td>Systemic shock</td>
</tr>
<tr>
<td>Coagulation abnormalities:</td>
</tr>
<tr>
<td>- Coagulation results (if obtained) outside the normal range</td>
</tr>
<tr>
<td>- Platelet count &lt;100 x 10⁹/L</td>
</tr>
<tr>
<td>- Anticoagulant therapy</td>
</tr>
<tr>
<td>Local infection at the lumbar puncture site</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
</tr>
<tr>
<td>Suspected meningococcal septicaemia (extensive or spreading purpura)</td>
</tr>
</tbody>
</table>


There is no agreement on the depth of coma that necessitates imaging before lumbar puncture; some argue Glasgow coma score <12, others Glasgow coma score <9.

Patients on warfarin should be treated with heparin instead, and this stopped before lumbar puncture.

Consider imaging before lumbar puncture in patients with known severe immunocompromise (e.g. advanced HIV).

A lumbar puncture may still be possible if the platelet count is 50 x 10⁹/L; Seek haematological advice.

in addition to histology to define many tumour entities (Louis et al. 2016). Partly as a consequence it presents a major restructuring of the diffuse gliomas, medulloblastomas and other embryonal tumours and incorporates new entities (Table 14.5). These will be described here under the heading of the specific tumour type. 2016 WHO CNS classification also deletes a number of former entities including gliomatisis cerebri, protoplasmic and fibrillary astrocytomas, cellular ependymomas and primitive neuro-ectodermal tumours.

Pathological diagnosis may be difficult; some tumours may contain histologically different areas and biopsy diagnosis may, therefore, not give the full diagnostic picture. It is also essential to realise that the clinical prognostic significance of pathological grading and, to a lesser extent, staging may be different from its biological value. A benign tumour that is strategically located, for example, an optic pathway tumour with its risk of causing blindness, may not be removable without worsening

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### Table 14.5  WHO classification of tumours of the central nervous system

<table>
<thead>
<tr>
<th>Diffuse astrocytic and oligodendrogial tumours</th>
<th>Neuronal and mixed neuronal-glial tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma, IDH-mutant</td>
<td>Dysembryoplastic neuroepithelial tumour</td>
</tr>
<tr>
<td>Gemistocytic astrocytoma, IDH-mutant</td>
<td>Gangliocytoma</td>
</tr>
<tr>
<td>Diffuse astrocytoma, IDH-wildtype</td>
<td>Ganglioglioma</td>
</tr>
<tr>
<td>Diffuse astrocytoma, NOS</td>
<td>Anaplastic ganglioglioma</td>
</tr>
<tr>
<td>Anaplastic astrocytoma, IDH-mutant</td>
<td>Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma, NOS</td>
<td>Desmoplastic infantile astrocytoma and ganglioglioma</td>
</tr>
<tr>
<td>Glioblastoma, IDH-wildtype</td>
<td>Papillary glioneuronal tumour</td>
</tr>
<tr>
<td>Giant cell glioblastoma</td>
<td>Rosette-forming glioneuronal tumour</td>
</tr>
<tr>
<td>Gliosarcoma</td>
<td>Diffuse leptomeningeal glioneuronal tumour</td>
</tr>
<tr>
<td>Epithelioid glioblastoma</td>
<td>Central neurocytoma</td>
</tr>
<tr>
<td>Glioblastoma, IDH-mutant</td>
<td>Extraventricular neurocytoma</td>
</tr>
<tr>
<td>Glioblastoma, NOS</td>
<td>Cerebellar liponeurocytoma</td>
</tr>
<tr>
<td>Diffuse midline glioma, H3 K27M-mutant</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td>Oligodendroglia, IDH-mutant and 1p/19q-codeleted</td>
<td>8693/3</td>
</tr>
<tr>
<td>Anaplastic oligodendroglia, IDH-mutant and 1p/19q-codeleted</td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma, NOS</td>
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<tr>
<td>Anaplastic oligoastrocytoma, NOS</td>
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<tr>
<td>Other astrocytic tumours</td>
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<td>Pilocytic astrocytoma</td>
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<tr>
<td>Pilomyxoid astrocytoma</td>
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<tr>
<td>Subependymal giant cell astrocytoma</td>
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<tr>
<td>Pleomorphic xanthoastrocytoma</td>
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<tr>
<td>Anaplastic pleomorphic xanthoastrocytoma</td>
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<tr>
<td>Ependymal tumours</td>
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<tr>
<td>Subependymoma</td>
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<tr>
<td>Myxopapillary ependymoma</td>
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<td>Ependymoma</td>
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<td>Papillary ependymoma</td>
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<td>Clear cell ependymoma</td>
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<td>Tanycytic ependymoma</td>
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<tr>
<td>Ependymoma, RELA fusion–positive</td>
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<tr>
<td>Anaplastic ependymoma</td>
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<td>Other gliomas</td>
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<td>Chordoid glioma of the third ventricle</td>
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<td>Angiocentric glioma</td>
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<td>Astroblastoma</td>
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<td>Choroid plexus tumours</td>
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<td>Choroid plexus papilloma</td>
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<td>Atypical choroid plexus papilloma</td>
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<tr>
<td>Choroid plexus carcinoma</td>
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<td>Tumours of the pineal region</td>
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<td>Pineocytoma</td>
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<tr>
<td>Pineal parenchymal tumour of intermediate differentiation</td>
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<tr>
<td>Pineoblastoma</td>
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<tr>
<td>Papillary tumour of the pineal region</td>
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<tr>
<td>Embryonal tumours</td>
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<tr>
<td>Medulloblastomas, genetically defined</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma, WNT-activated</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma, SHH-activated and TP53-mutant</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma, SHH-activated and TP53-wildtype</td>
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<td>Medulloblastoma, non-WNT/non-SHH</td>
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<td>Medulloblastoma, group 4</td>
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<td>Medulloblastomas, histologically defined</td>
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<td>Medulloblastoma, classic</td>
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<tr>
<td>Medulloblastoma, desmoplastic/nodular</td>
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<tr>
<td>Medulloblastoma with extensive nodularity</td>
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<tr>
<td>Medulloblastoma, large cell/anaplastic</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma, NOS</td>
<td></td>
</tr>
<tr>
<td>Embryonal tumour with multilayered rosettes, C19MC-altered</td>
<td></td>
</tr>
<tr>
<td>Embryonal tumour with multilayered rosettes, NOS</td>
<td></td>
</tr>
<tr>
<td>Medulloepithelioma</td>
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<tr>
<td>CNS neuroblastoma</td>
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<td>CNS ganglioneuroblastoma</td>
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<tr>
<td>CNS embryonal tumour, NOS</td>
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</tr>
<tr>
<td>Atypical teratoid/rhabdoid tumour</td>
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<tr>
<td>CNS embryonal tumour with rhabdoid features</td>
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Continued
### Table 14.5  WHO classification of tumours of the central nervous system (continued)

<table>
<thead>
<tr>
<th>Classification</th>
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<tr>
<td>Tumours of the cranial and paraspinal nerves</td>
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<tr>
<td>Schwannoma</td>
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<td>Melanotic schwannoma</td>
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<td>Hybrid nerve sheath tumours</td>
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<td>Malignant peripheral nerve sheath tumour (MPNST)</td>
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<td>Epithelioid MPNST</td>
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<td>MPNST with perineurial differentiation</td>
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<td>Meningiomas</td>
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<td>Meningioma</td>
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<tr>
<td>Meningothelial meningioma</td>
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<td>Transitional meningioma</td>
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<td>Clear cell meningioma</td>
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<td>Mesenchymal, non-meningothelial tumours</td>
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<td>Grade 2</td>
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<tr>
<td>Grade 3</td>
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<td>Angiosarcoma</td>
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<td>Kaposi sarcoma</td>
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<td>Ewing sarcoma/PNET</td>
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<td>Inflammatory myofibroblastic tumour</td>
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<td>Fibrosarcoma</td>
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<td>Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma</td>
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<td>Leiomyoma</td>
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<td>Leiomyosarcoma</td>
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<td>Rhabdomyoma</td>
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<tr>
<td>Rhabdomyosarcoma</td>
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<td>Chondrosarcoma</td>
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<td>Osteochondroma</td>
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<td>Osteosarcoma</td>
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<td>Lymphomas</td>
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<td>Diffuse large B-cell lymphoma of the CNS</td>
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<td>AIDS-related diffuse large B-cell lymphoma</td>
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<td>EBV-positive diffuse large B-cell lymphoma, NOS</td>
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<td>Lymphomatoid granulomatosis</td>
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<td>Intravascular large B-cell lymphoma</td>
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<td>Low-grade B-cell lymphomas of the CNS</td>
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<td>T-cell and NK/T-cell lymphomas of the CNS</td>
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<td>Anaplastic large cell lymphoma, ALK-positive</td>
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<tr>
<td>Anaplastic large cell lymphoma, ALK-negative</td>
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<td>MALT lymphoma of the dura</td>
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<td>Histiocytic tumours</td>
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<tr>
<td>Langerhans cell histiocytosis</td>
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<td>Erdheim–Chester disease</td>
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<td>Rosai–Dorfman disease</td>
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<td>Juvenile xanthogranuloma</td>
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<td>Histiocytic sarcoma</td>
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<td>Germ cell tumours</td>
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<td>Germinoma</td>
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<td>Embryonal carcinoma</td>
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</tr>
<tr>
<td>Yolk sac tumour</td>
<td>9071/3</td>
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*Continued*
seen as standard practice in many units. The use of neuroendoscopy is particularly suited for the management of hydrocephalus associated with brain tumours, biopsy/resection of ventricular tumours, inspection of the tumour bed for residual following tumour resection, and for skull base tumours. Intra-operative ultrasound allows quick localisation of tumour intraoperatively and is useful for monitoring progress during surgery. Intra-operative MRI is available in a number of institutions and is particularly useful in the management of very large tumours. A good review of the intra-operative adjunctive imaging techniques can be found in Schmidek and Sweet (Quinones-Hinojosa 2012).

**Radiation Therapy**

Radiation therapy remains the most effective adjuvant therapy for brain tumours. Ionising radiation disrupts DNA replication during cell division leading to cell death and is therefore most effective in rapidly dividing cells of tumours. Dosing is critical as the effects on the tumour DNA may also affect normal tissues, particularly in early life when cell division is a normal feature (e.g. in the hippocampus, the blood vessel intima, the cranium and spinal vertebra).

Radiation can be delivered in a single fraction or in small fractions given at intervals 2 or 3 days apart, daily or ‘hyper-fractionated’ that is, two (or, in theory, more) doses per day separated by an interval of at least 6 hours. Dose fractionation determines the ratio of tumour cytotoxicity in ‘early reacting’ tissues (e.g. tumours) to that in ‘late reacting’ tissues (e.g. CNS). This ratio increases with decreasing fraction size. Smaller fractions and hyperfractionated schedules can therefore enable the use of higher doses that are more cytotoxic to the tumour without increasing toxic effects on the CNS. The total dose is the cumulative sum of radiation fractions delivered to the fields involving the tumour and remote sites at risk of tumour spread.

Radiation can be applied to infinitely variable shaped fields involving the primary tumour alone or in extended fields including whole brain and spine to include the CSF compartment. Targeting of radiotherapy precisely to anatomical regions is achieved with cumulative dosing within precisely shaped overlapping fields and in schedules tailored to particular therapeutic needs. Techniques which permit the radiation fields to be specifically shaped to the tumours three-dimensional profile include tomotherapy, and intensity-modulated, stereotactic and gamma knife radiotherapy. These methods all deliver photon beams that are precisely anatomically targeted by different types of machines.

Radiation can also be delivered by heavy ions (e.g. carbon ions) or by proton or neutron beams but the use of last of these is limited by serious associated toxicities. Proton therapy, in particular, has recently been the focus of significant development. The use of proton beam radiotherapy also delivers X-rays but offers the theoretical advantage of delivery of the majority of the dose in the last centimetre of a defined path of the particles, known as the Bragg peak, without delivery to tissues distal to the Bragg peak (Fig. 14.5) thus reducing toxicity from the exit dose. Proton beams can, for example, be delivered to the thoracic spinal cord with relatively less irradiation of cardiac tissues (Figs 14.6a and b). However, proton beams can also have limitations when used over large volumes and may also be associated with a greater risk of certain short term toxicities (e.g. over- or under-treatment of the interface between two overlapping fields).

In childhood, the unwanted effects of radiotherapy on the CNS, somatic growth and other tissues are greater the younger the patient. Where the tissue is cortical tissue, cognitive function can be damaged, affecting particularly short term memory, attention span, and processing speed. If this occurs very early in life, it decreases the rate at which new skills can be acquired leading to an apparent ‘drop off’ in IQ because the IQ scale is normalised to the rate of acquisition of new skills in typically developing children. Where the tissues are endocrine the physiological control mechanisms of hormone secretion are affected and result in progressive hormone failure. Radiation also damages blood vessel...
Chapter 14  Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri

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**Figure 14.5** Depth–dose distributions for a spread-out Bragg peak (SOBP; red), its constituent pristine Bragg peaks (blue), and a 10MV photon beam (black). The SOBP dose distribution is created by adding the contributions of individually modulated pristine Bragg peaks. The penetration depth, or range, measured as the depth of the distal 90% of plateau dose, of the SOBP dose distribution is determined by the range of the most distal pristine peak (labelled ‘Pristine peak’). The modulation width, measured as the distance between the proximal and distal 90% of plateau dose values, of the SOBP dose distribution is controlled by varying the number and intensity of pristine Bragg peaks that are added, relative to the most distal pristine peak, to form the SOBP. The dashed lines (black) indicate the clinical acceptable variation in the plateau dose of 72%. The dot–dashed lines (green) indicate the 90% dose and spatial, range and modulation width, intervals. The SOBP dose distribution of even a single field can provide complete target volume coverage in depth and lateral dimensions, in sharp contrast to a single photon dose distribution; only a composite set of photon fields can deliver a clinical target dose distribution. Note the absence of dose beyond the distal fall-off edge of the SOBP (Reproduced from Levin et al. (2006) Proton beam therapy. British Journal of Cancer 93: 849–54, with kind permission of Nature Publishing Group).

**Figure 14.6** Comparison of radiation dosimetry in craniospinal irradiation delivered by three dimensional conformal photon radiotherapy; volumetric-modulated arc therapy (VMAT, an advanced form of intensity-modulated photon radiotherapy); and proton beam radiotherapy (PBT); (a) axial views; (b) sagittal views. The colour coding key indicates the fields receiving low (blue), intermediate (green/yellow) and high doses (red) of radiation. Note that the three methods deliver rather similar doses to the (large) cranial field but that proton therapy delivers therapeutic doses to the (small) spinal fields while exposing heart, lung and kidney to the lowest radiation doses. (Courtesy of Dr Nicky Thorp, The Clatterbridge Cancer Centre NHS Foundation Trust, The Wirral, UK.)

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**Cytotoxic Chemotherapy**

The use of cytotoxic chemotherapy has a long history and is established in both benign and malignant CNS tumours. Its effects on brain tumour are dependent upon the sensitivity of the tumour to the drug’s effect and the tissue levels that can be achieved via oral or intravenous administration. Direct administration to the CSF, tumour cavity or tumour...
interstitium can achieve responses with drastically reduced systemic doses and thus avoid unwanted systemic effects. The many and various unwanted effects of chemotherapy on the CNS have been reviewed by Kennedy and Nicolin (2013). Pre- or post-surgery chemotherapy can be used to complement neurosurgery by debulking the tumour. It can also be used either as an adjuvant therapy to consolidate remission and eradicate tumour, or in a continuing schedule to defer irradiation in very young children, or in very high-dose regimens requiring haematological stem cell rescue techniques to achieve transiently elevated drug levels within the brain. However, the systemic toxicity of the latter approach is high and life threatening and its benefit remains unproven. Its neurotoxic effects, especially in conjunction with maximised radiation therapy dosing are not completely understood despite extensive trials (Vivekanandan et al. 2015). The use of intrathecal chemotherapy to control leptomeningeal disease with minimal side effects has an established role in acute leukaemias and is increasing in CNS tumours. Delivering drugs directly to the tumour cavity is also an established technique (e.g. the use of gliadel wafers in high-grade glioma). Experimental approaches delivering drugs interstitially using continuous infusions are under investigation (Lewis et al. 2016).

For systemically administered cytotoxic chemotherapy, unwanted effects are prominent, particularly nausea, vomiting and other gastro-intestinal toxicities, bone marrow suppression and immunodeficiency, infertility, particularly in males, neuropathy, cardiac, renal and hearing toxicities. Furthermore, its dose-related DNA damaging effects can contribute to the risk of second tumours such as acute leukaemias, meningiomas, high-grade gliomas and sarcomas.

To date the only cytotoxic drugs licensed for primary CNS tumours in children or adults by the European Medicines Authority (EMA) are lomustine (CCNU) Temozolomide and Gliadel wafers, all in the management of high-grade glioma. In the US the Federal Drugs Administration (FDA) have also licensed Bevacizumab for high-grade glioma. The other drugs in current use are ‘off label’.

**Biologically Targeted Therapies**

The explosion of scientific information about tumour biology offers potential for targeted treatments. In children, this is exemplified by the use of mTOR inhibitors such as Rapamycin, originally developed as immunosuppressive drugs used in organ transplantation, for treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis. Their mechanism of action is linked to the mutated pathway characteristic of tuberous sclerosis complex (TSC). A randomised trial of Rapamycin has demonstrated tumour response to the drug as well as other beneficial effects on facial tubers and the drug Everolimus is now licensed for children with subependymal giant cell astrocytoma. At the time of writing there are no other drugs with a license for use that target mutated pathways in childhood brain tumours, although a number are the focus of great interest, particularly drugs targeting the mitogen n-activated protein kinase (MAPK) pathway in pilocytic astrocytoma, the commonest benign tumour of childhood. The use of such bio-targeted therapies to tackle malignant tumours has not yet been shown to be effective. The challenge is to test drugs in patient groups with known biological characteristics in sufficient numbers to make observations with sufficient reliability to satisfy licensing requirements. This is difficult in extremely rare conditions in young children. Without licensing, health systems are understandably reluctant to fund the use of these new and frequently very expensive drugs.

**Clinical Trials**

There is an active programme of clinical trials worldwide focused in the larger continents of North and South America, Asia and Europe. Large ‘phase 3’ trials exploring treatment programmes that combine surgery, radiotherapy and chemotherapy have contributed substantially to the progressive improvement in survival rates that has occurred over the last 30 years in childhood cancer generally and, to a lesser extent, in CNS tumours. The associated programmes of biological research have now identified a series of tumour subgroups justifying stratification for future trials. Inclusion in trials and research as part of primary treatment has been demonstrated to enhance standards of care and outcomes but the challenge, increased by more precise delineation of molecular subgroups, is to design trials that will recruit sufficient patients to generate the evidence.

**QUALITY OF SURVIVAL AND NEUROLOGICAL SEQUELAE OF BRAIN TUMOURS IN CHILDREN**

The results of recent advances in therapy have been impressive, especially for certain types of tumours that were often fatal a few years ago, such as medulloblastomas. CNS tumours and their treatments may, however, cause acute and chronic adverse effects. In particular, surgery, cranial irradiation and chemotherapy may induce damage to adjacent healthy tissues leading to neurological damage (reviewed in Bull and Kennedy 2013) for which, once it has occurred, there are few effective treatments. The natural history of healing within the CNS is supported by generic neuro-rehabilitation to promote the processes whereby healing or undamaged areas take over impaired functions. It is difficult to distinguish clearly the morbidities of chemotherapy and those of radiotherapy as the two modalities are often given together and several pathologies are caused by both (e.g. leukoencephalopathy – see below).

Treatment-related injury may appear early or late and may be temporary or permanent. Distinguishing direct effects of tumour those of treatment requires assessment of timing and cranial imaging, including radiation field maps. Adverse effects include neurological, visual and auditory deficits,
seizures, chronic pain including headache, cognitive impairment, neuro-endocrine dysfunction (including short stature due to growth hormone deficiency and spinal irradiation and deficiencies of other pituitary and effector organ hormones leading to hypothyroidism, hypogonadism and reduced fertility), stroke, and secondary malignancies (mostly meningiomas and gliomas, 2–40 years) after irradiation. This was reviewed by Wells and Kennedy (2017) from which some of the material below is drawn. Sequelae that develop or persist more than 5 years after tumour diagnosis, reviewed by Armstrong (2010), are often referred to as ‘late effects’ although the use of this cut-off point between ‘early’ and ‘late’ is somewhat arbitrary. Increased recognition of these problems has led to attempts to reduce or replace radiation therapy with various chemotherapeutic regimens (Kalifa and Grill 2005), to stratify treatment according to the risks of recurrence and of sequelae.

Tools to Assess Sequelae
Assessment tools for use in infants, children and young people have been developed and validated in the fields of oncology, neurology and cognition and are used with increasing standardisation across studies. The WHO Classification of Functioning, Disability and Health (ICF) has been validated in childhood brain tumour survivors (Khan and Amatya 2013) and should remain the context within which outcome measures are placed. For patients receiving treatment on a study protocol, neurological sequelae are reported using Common Terminology Criteria for Adverse Events (current version 4.0; https://evs.nci.nih.gov/ftp1/CTCAE/About.html) which provides standardised grading of adverse effects including endocrine and nervous system symptoms, based on clinician assessments with either a 3- or 5-point severity scale. The Neurological Predictor Scale (Micklewright et al. 2008) was developed to serve as a cumulative index of a child’s exposure to risk factors but is not widely implemented. A degree of consensus has been achieved in both Europe (Limond et al. 2015) and North America (Embry et al. 2012) regarding practicable approaches to assessing quality of survival, including health-related quality of life, that involves administration of not only questionnaires for parents and patients but also short batteries of direct psychometric assessments.

A major advance has been the use of computerised batteries for neurocognitive assessment, including the CANTAB and CogState. The NIH toolbox (Weintraub et al. 2013) and the Patient Reported Outcome Measurement Information System (PROMIS) (Hinds et al. 2013) are relatively newly validated tools for quality of survival assessments. These tools and others are increasingly utilised as quality of survival measures in prospective treatment studies.

IQ testing using the Wechsler Intelligence Scales (WISC), most recently WISC-V (Canivez et al. 2016), has been the most common means to measure neurocognitive deficit in children treated for brain tumours. All the WISC scores are scaled so that the mean and standard deviation of scores in the general population are 100 and 15 respectively. Test scores are constructed in such a way that the IQ is not expected to change substantially over time in that population. The temptation to express neurocognitive outcome as a single number that ‘summarises’ outcome and is known to have a normal distribution in the healthy population is overwhelming for many investigators. There are several limitations of IQ when used in this way. First, IQ may not indicate subtle but important deficits: important neurocognitive deficits may coexist with a normal IQ. Specific deficits in selective attention and executive function with normal IQ, for example, are typical findings in children treated for supratentorial hemispheric pilocytic astrocytomas treated with surgery alone (Aarsen et al. 2009). This problem can be overcome with more sophisticated, in-depth assessment.

Second, IQ score will not capture several important aspects of quality of survival such as ability to live independently. Indeed the difficulty in predicting from IQ scores which individuals with intellectual impairment could and could not live independently provided the impetus for the development of Adaptive Behaviour Scales (e.g. Sparrow et al. 2005) that measure typical abilities in everyday living as assessed by a third party rather than testing intellectual abilities by direct testing. No amount of neurocognitive assessment can avoid this difficulty.

Third, the evaluation of neurocognitive function requires direct assessment by a qualified assessor. This is resource intensive and makes considerable demands on the survivor. Consequently, reports on neurocognitive deficits are typically limited by being obtained only in convenience samples at single institutions or from multi-centre samples with high attrition rates. They are, therefore, of doubtful generalisability. Analysis of a group in which more impaired survivors are selectively retained in a study, for example, may be misinterpreted as a fall-off in ability in individuals in the group.

IQ is itself dependent on underlying core cognitive functions and the structure of the most recent versions IV and V of the WISC were influenced by Carroll’s three stratum theory of cognitive abilities (Carroll 2003) which identifies the core factors that contribute to IQ scores. Full Scale IQ represents a child’s general intellectual ability ($g$) and, in the WISC-IV and WISC-V, is comprised of four broad domains of cognitive abilities: verbal comprehension, perceptual reasoning, working memory, and processing speed (Canivez et al. 2016). These core cognitive functions provide the foundations of effective learning and retention of information underlying $g$ in Stratum III of the Carroll model and can be mapped on to the eight broad cognitive abilities in Stratum II. These are fluid intelligence, crystallised intelligence, visual perception, auditory perception, general memory and learning, long-term storage and retrieval, cognitive processing speed and reaction speed. Improvements in memory and processing speed together account for almost half of age-related improvements in IQ (Fry and Hale 1996).

By contrast to IQ assessment, other aspects of assessment of quality of survival are more amenable to population-based indirect assessment by questionnaire (Boman et al. 2009a, b;
specific neurological sequelae of brain tumours

The incidence of motor or coordination problems is highest at presentation and during initial treatment. In the acute post-treatment period, weakness may result from perioperative injury, oedema or stroke. A large epidemiological study found that 4.6% of long-term survivors developed motor problems at least 5 years after treatment and their relative risk of doing so was 12.5 times that of unaffected siblings with a doubling of risk in those that had received 50 Gy or more of radiation to the frontal lobes (Packer et al. 2003). Weakness may also result from myelopathy from spinal radiation therapy or chemotherapy, particularly if intrathecal, and may be accompanied by bowel or bladder dysfunction and sensory deficits, depending on location and severity (Chukwu et al. 2015).

Seizures occur as part of the presentation of a brain tumour in about a quarter of cases, with low grade indolent tumours being the tumour type most likely to present in this way, and continue after primary treatment in about 15% (Van Breenen et al. 2007). New onset or worsening of seizures post treatment may signify tumour progression or recurrence, treatment-related neurotoxicity, low drug levels or metabolic disturbance. Non enzyme-inducing antiepileptic drugs are preferred to avoid interactions with chemotherapy (Ruggiero et al. 2010). Seizures occurring in the early postoperative period are often transient provoked seizures rather than epilepsy and should not routinely be treated with post-discharge anticonvulsants. The hypothesis that sodium valproate has valuable anti-tumour effects is unproven and should not influence choice of anticonvulsant. Antiplatelet effects of anticonvulsants may be a relative contraindication in some patients because of antiplatelet effects of anti-tumour treatments. A trial of withdrawal of antiepileptic medication is often deferred until a patient has been seizure-free for 2 years but adverse CNS effects of anticonvulsants may lead to important functional deficits when added to the effects of the tumour and anti-tumour treatments.

Acute Encephalopathy

The posterior reversible encephalopathy syndrome (PRES) has been reported in association with cisplatin, cytarabine, cyclosporins, cyclophosphamide, methotrexate, rituximab, paclitaxel, and other chemotherapies. Presenting symptoms consist of headache, visual disturbances, seizures which may be intractable and require aggressive acute therapy, nausea and vomiting, altered cognitive status, and, in some cases, focal deficits (McCoy et al. 2011). PRES is usually associated with hypertension or hypotension, sometimes in association with metabolic abnormalities. The neurological deficit is usually reversible upon regulation of blood pressure and withdrawal of chemotherapy. High-dose arabinosyl cytosine (Ara-C), ifosfamide and methotrexate are also known to cause subacute neurotoxicity with headaches, seizures, auditory and visual hallucinations, visual disturbances, pseudobulbar palsy, extrapyramidal signs and paresis.

Another cause of encephalopathy with focal neurological deficits is tumour pseudoprogression resulting from treatment-induced tumour and peri-tumoural tissue oedema. This may present as progressive neurological deterioration with cerebral oedema on imaging, typically 6 weeks to 3 months after radiation therapy. Concurrent treatment with chemotherapy may be a risk factor. When symptomatic, the condition is treated with high-dose corticosteroids. Bevacizumab is increasingly employed for patients who experience rapid deterioration despite corticoid therapy and/or intolerable steroid side effects (Preuss et al. 2013).

The stroke-like migraine after radiation therapy (SMART) syndrome causes acute or subacute focal impairment, often accompanied by encephalopathy and headache. It may be associated with hypointensities on susceptibility-weighted imaging (SWI) and gyriform enhancement on T1-weighted MRI. SWI may help distinguish SMART from other conditions that may have a similar post-contrast MRI appearance (Khanipur et al. 2015). Treatment includes the use of hydration and neuroprotective measures including avoidance of hypotension.

Cerebrovascular complications in childhood CNS tumour survivors include large-vessel vascular injury, stroke, moyamoya (Ullrich et al. 2007), mineralising microangiopathy, cavernomas and other vascular malformations, and stroke-like migraines. The incidence of neurovascular events in childhood brain tumour survivors has been found to be 100-fold higher than in the general paediatric population (Campen et al. 2012). Cranial irradiation, particularly to the circle of Willis, is an important risk factor for stroke and cerebrovascular abnormalities, and the risk is dose-dependent (Bowers et al. 2006; Campen et al. 2012; Mueller et al. 2013). Chemotherapy including methotrexate, anthracyclines, mitomycins, asparaginase (especially venous sinus thrombosis) and anti-vascular endothelial growth factor (VEGF) may also increase risk (DiGiannatale et al. 2014). Asymptomatic radiographic findings include micro-bleeds and superficial siderosis, and all events are more common in children who received whole-brain radiation (Passos et al. 2015). A study
of young adults with radiation induced cavernous malformations (RICMs) found that they occurred within the radiation field on average 12 years after radiation treatment. Compared with non-radiation cavernous malformations, RICMs were more likely to occur as multiple cavernous malformations, to present at a younger age, and were at least as likely to cause symptomatic haemorrhage (Cutsforth-Gregory et al. 2015).

**Peripheral Neuropathy**

Lower motor neuron weakness may result from toxicity from chemotherapy, in particular vinca alkaloids (vincristine), platinum drugs (cisplatin, oxaliplatinum, carboplatin), methotrexate, and some biological agents, including those with antiangiogenic properties. Chemotherapy-induced peripheral neuropathy may be pure sensory (e.g. diminished temperature and vibratory sensation, burning paraesthesiae, jaw pain), predominantly motor (e.g. foot drop), and/or have an autonomic component that includes constipation and orthostatic hypotension. Symptoms are dependent on the duration and dose of drug therapy and their severity varies from subclinical through mild discomfort to severely debilitating symptoms and signs. The neuropathy is often worse in older individuals. Attempts to prevent or treat have failed, with the exception of medications for hyperaesthesia and pain control. A patient-report rating scale for neuropathy has been validated and is reported to be sensitive to clinical important Vincristine-induced deficits (Lavoie Smith et al. 2015). Platinum drugs also cause auditory neuropathy and audiograms are required to monitor this, often dose-limiting, unwanted effect. Molecular genetic predictors such as alterations in CYP5a enzymes may provide criteria for adapting treatment according to genetic risk to reduce the incidence of drug-induced hearing loss.

**SPECIFIC FEATURES OF BRAIN TUMOURS IN INFANTS AND CHILDREN**

**Brain Tumours in Infants and Children Under 2 Years of Age**

These differ in regional distribution, pathology, clinical features and therapy from those of older children. The proportion of all childhood brain tumours occurring at this age may be at least 10%. A significant number of these are definite ‘congenital’ tumours, that is, they produce symptoms within the first 2 weeks of life, or ‘probably congenital’ tumours, that is, they are present or recognised within the first year of life (Sarkar et al. 2005).

The Surveillance, Epidemiology and End Results Data (SEER) USA database would suggest that gliomas represented 42.5% of brain tumours in infants under 12 months of age (Bishop et al. 2012). Of these gliomas, 43% were low grade histology, of which about half were pilocytic astrocytomas, 24% were high grade and 33% were unspecified malignant glial tumours without a documented grade. Medulloblastomas, ependymomas and germinomas accounted for 16.2%, 10.5% and 5.0% of cases respectively. Infants with low grade gliomas had the highest observed survival of 85.6% at 3 years, whereas those with atypical teratoid/rhabdoid tumours (ATRTs) or
primary rhabdoid tumours of the brain had the lowest, with a 1-year survival of 39.7%. Median 3-year survival estimates for other groups were 72% for choroid plexus tumours, 60% for germ cell tumours, 52% for high-grade gliomas, 35% for supratentorial primitive neuroectodermal tumours (PNETs) (termed embryonal tumour with multilayered rosettes in the WHO classification), and 30% for medulloblastoma (Louis et al. 2016).

The clinical features of congenital and early-onset tumours vary with the type and location of the tumour. Macrocrania, delayed milestones and behavioural disturbances are common presenting clinical features. In the case of congenital tumours, fetal deaths and preterm births are frequent. Intracranial haemorrhage can be the presenting manifestation. Vomiting, focal neurological signs, seizures and the diencephalic syndrome of emaciation (see below) may also be early signs. Infantile spasms are an uncommon manifestation.

The diagnosis may be delayed if the significance of relatively nonspecific clinical features, such as delayed milestones or vomiting, is not recognised. Tumours manifested by hemiplegia may be difficult to distinguish from congenital static hemiplegia but brain imaging will resolve any doubt. CSF examination may be misleading as pleocytosis and increased protein are commonly found. CT and MRI will, in most cases, readily permit the diagnosis.

Historically, the prognosis of congenital tumours is poor (Sarkar et al. 2005). Many tumours are malignant. Surgery is difficult because of the large size of many tumours and the small circulating volume of blood. Staged resections may reduce the mortality risk. Radiation is highly dangerous for the very young developing brain and its use has declined since 1979 (Bishop et al. 2012). The power of radiotherapy both to confer substantial benefit to survival rates and also to cause severe long-term sequelae by late effects on the CNS and other organs frequently poses difficult dilemmas in this age group especially as the results of prolonged regimens of adjuvant chemotherapy have been ‘underwhelming’ with a high risk of disease progression at 12–18 months (Bishop et al. 2012). Moreover, the possible late effects of chemotherapy are as yet poorly known. Some role for focal radiotherapy is now being rediscovered following evidence of lack of severe long-term sequelae in the treatment of ependymoma (Merchant et al. 2010).

Quality of life (QoL) for survivors of infant brain tumours is often poor as illustrated by a follow-up study of 27 consecutively treated patients diagnosed in the first year of life in a single centre in Switzerland. Persistent neurological complications occurred in nine out of 11 survivors, endocrine and growth complications in four out of 11, and cognitive deficits leading to school problems/impaired choice of occupation in eight out of ten. Behavioural and psychological adjustment problems were reported by four of six patients and seven out of ten parents. HRQoL as rated by patients and their parents was considerably lower than that of healthy controls. In comparison with healthy controls, social functioning was rated by the patients and the parents as the QoL dimension most affected. HRQoL was lowest for patients with high-grade tumour histology and more intense therapy (Gerber et al. 2008).

CHARACTERISTICS OF INDIVIDUAL TUMOURS

The localisation and histology (in the now obsolete CNS 2007 WHO classification) of the major types of brain tumours are shown in Figures 14.2a and 14.2b respectively.

POSTERIOR FOSSA TUMOURS

MEDULLOBLASTOMA

INcidence

Medulloblastoma accounts for 14–20% of childhood intracranial tumours and is second only to cerebellar astrocytoma among posterior fossa tumours. Medulloblastoma is most frequent in the first decade of life and twice as common in boys as in girls. It has been reported in the neonatal period.

PATHOBIOLoGY OF MEDULLOBLASTOMA

Medulloblastoma is a malignant and rapidly growing tumour arising from undifferentiated neural cells. The tumour is poorly demarcated from normal tissue. It is very cellular and consists of small round cells without any definite pattern, with frequent mitotic figures. Medulloblastomas usually arise from the cerebellar vermis in the region of the roof of the fourth ventricle but the attachment can extend along the cerebellar peduncles and along the floor of the IVth ventricle. They extend toward the dorsum of the cerebellar vermis and into the lumen of the fourth ventricle thus producing hydrocephalus. Metastases along the CSF pathways are frequent, and imaging of the spinal canal is important to determine the extent of the tumour. Extraneural metastases, which occur only rarely in cases treated surgically, involve spread to bone and lymphoid tissues.

The precise histological classification of medulloblastoma is difficult because of its primitive nature. It is distinct from other embryonal tumours of the CNS and the term primitive neuro-ectodermal tumour has been removed entirely from the histological lexicon in WHO CNS 2016. Histological variants of medulloblastoma (e.g. desmoplastic/nodular, medulloblastoma with extensive nodularity, large cell, anaplastic) relate to molecularly defined subgroupings and to prognosis (Rutkowski et al. 2010; Louis et al. 2016) (Table 14.6). Identification of PTCH1 mutation in sporadic medulloblastoma revealed the role of the ‘sonic hedgehog’ (SHH) pathway mutations.
Table 14.6 Summary of the most common medulloblastoma integrated diagnoses with clinical correlates

<table>
<thead>
<tr>
<th>Genetic profile</th>
<th>Histology</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma, WNT activated</td>
<td>Classic</td>
<td>Low-risk tumour, classic morphology found in almost all WNT-activated tumours</td>
</tr>
<tr>
<td></td>
<td>Large cell/anaplastic (very rare)</td>
<td>Tumour of uncertain clinicopathological significance</td>
</tr>
<tr>
<td>Medulloblastoma, SHH-activated, <em>TP53</em>-mutant</td>
<td>Classic</td>
<td>Uncommon high-risk tumour</td>
</tr>
<tr>
<td></td>
<td>Large cell/anaplastic</td>
<td>High-risk tumour, prevalent in children aged 7–17 years</td>
</tr>
<tr>
<td></td>
<td>Desmoplastic/nodular (very rare)</td>
<td>Tumour of uncertain clinicopathological significance</td>
</tr>
<tr>
<td>Medulloblastoma, SHH-activated, <em>TP53</em>-wildtype</td>
<td>Classic</td>
<td>Standard-risk tumour</td>
</tr>
<tr>
<td></td>
<td>Large cell/anaplastic</td>
<td>Tumour of uncertain clinicopathological significance</td>
</tr>
<tr>
<td></td>
<td>Desmoplastic/nodular</td>
<td>Low-risk tumour in infants; prevalent in infants and adults</td>
</tr>
<tr>
<td></td>
<td>Extensive nodularity</td>
<td>Low-risk tumour of infancy</td>
</tr>
<tr>
<td>Medulloblastoma, non-WNT/non-SHH, group 3</td>
<td>Classic</td>
<td>Standard-risk tumour</td>
</tr>
<tr>
<td></td>
<td>Large cell/anaplastic</td>
<td>High-risk tumour</td>
</tr>
<tr>
<td>Medulloblastoma, non-WNT/non-SHH, group 4</td>
<td>Classic</td>
<td>Standard-risk tumour; classic morphology found in almost all group 4 tumours</td>
</tr>
<tr>
<td></td>
<td>Large cell/anaplastic (rare)</td>
<td>Tumour of uncertain clinicopathological significance</td>
</tr>
</tbody>
</table>


Genetic disruption of this pathway in medulloblastoma results in inappropriate activation of the signalling cascade and downstream tumourogenesis (Taipale and Beachy 2001). This and other advances in understanding of the molecular variation in medulloblastoma have led to wide acceptance that there are four genetic (molecular) groups of medulloblastoma WNT-activated, SHH-activated, and the numerically designated ‘group 3’ and ‘group 4’. Some of these histological and genetic variants are associated with dramatic prognostic differences and give rise to histologically and genetically defined ‘integrated diagnoses’ with clinical correlates (Table 14.6) (Louis et al. 2016).

Treatment intensity is now defined by the presence (‘high-risk’ disease) or absence (‘standard-risk’) of histological and genetic and clinical (postoperative tumour residue >1.5 cm³) [note that this is a measure of area, not volume] and/or metastatic disease at diagnosis. This stratification currently forms the basis of patient selection into clinical trials (Pizer and Clifford 2009). These ‘disease-wide’, that is, derived from high-, standard- and low-risk cases, biological markers of prognosis in medulloblastoma appear to have a different prognostic significance when applied to standard-risk patients. Specifically, although the favourable prognosis of WNT-activated medulloblastoma was confirmed, better outcomes were observed for other medulloblastoma variants in standard-risk medulloblastoma compared to previous disease-wide clinical trials (Clifford et al. 2015).

In addition to classification on the above schema, single medulloblastoma samples can be characterised into subgroups according to their minimal DNA-methylation signatures. These technologies are transferrable to many diagnostic laboratories. Importantly, the assay is applicable to limited and low-quality samples refractory to array-based analysis, allowing the retrospective unlocking of subgroup status in historical trials cohorts (Schwalbe et al. 2016).

Clinical features and imaging of medulloblastoma

The typical clinical presentation is with symptoms and signs of raised ICP in combination with ataxia. Symptoms of raised ICP are prominent and may be isolated. Ataxia is usually truncal or affects both lower limbs, with a tendency to fall backwards or forward. The whole symptomatology develops rapidly in a few weeks and papilloedema is often lacking. Bilateral pyramidal tract signs may be present. Occasionally, multiple cranial nerve involvement, spinal root pain or even paraplegia are seen early, indicating the presence of metastatic dissemination.

The imaging appearance of medulloblastoma on CT and MRI is highly suggestive. The tumour is midline and rounded and has, on unenhanced scans, a density slightly higher than or similar to the surrounding parenchyma. The density often increases homogeneously and markedly on contrast injection. In some cases, small cystic areas, haemorrhages or calcification are visible. Hydrocephalus is usually present (Fig. 14.8).

Treatment of medulloblastoma

Therapy of medulloblastoma begins with removal of the tumour, which should leave less than 1.5 cm³ of residual tumour.
Figure 14.8 Medulloblastoma: comparison with cerebellar astrocytoma. (In each pairing of images the left-hand scan is from a case of medulloblastoma and the right-hand scan from a case of cerebellar astrocytoma.) (a) Cerebellar medulloblastoma involving the vermis and compressing and invading the brainstem. MRI scan showing heterogeneous enhancement of the mass and hydrocephalus with dilatation of the temporal horns. (b) MRI scan of a different case illustrates the fact that some medulloblastomas can involve the cerebellar hemispheres and make differential diagnosis with cerebellar astrocytoma (a benign tumour) problematic.

The combination of this degree of resection with no metastatic spread to other parts of the CNS prior to surgery and classic histology (Table 14.6) constituting the 'standard-risk' profile and is associated with a better outlook than partial removal. It is not clear that complete excision is associated with lower survival rates than that associated with leaving a small residuum of less than 1.5cm² of residual tumour and it is noteworthy that the increase in incidence of cerebellar mutism coincides with the increase in the proportion of cases in whom complete excision is achieved.

Radiotherapy has a major role in extending survival rates. The use of high-energy sources and increased doses accounts for the recent marked increases in survival. Recommended doses are currently 50–55Gy to the posterior fossa and 35–4 Gy to the neuroaxis. Chemotherapy alone, with vincristine, cisplatin, nitrosourea or various combinations of alkylating agents such as CCNU, methotrexate, carmustine (BCNU), cisplatin and prednisone, appears to be effective and may be the treatment of choice for some subgroups of children under 2 years of age. Rutkowski (2006) used chemotherapy alone for treatment of young children, with a complete remission rate of 80%, and this method may become the rule for infants and young children.

Outlook of medulloblastoma
Considering all medulloblastomas diagnosed at age 0–19 years from 1973–2011, 5-year survival was 58% in the US SEER registry and of those in this age range followed up and surviving the first 5 years from diagnosis, 30-year overall survival and cancer-specific survival were also reduced at 70.2% and 80.1% respectively (Frandsen et al. 2015). However, when applying these numbers in the clinic currently, it is important to bear in mind that the 5-year survival rates for children with medulloblastomas have improved during the past two decades to around 80% for standard-risk patients. Patients with high-risk medulloblastoma (age less than 3 years, residual tumour greater than 1.5cm² of tumour, CSF or solid metastases) had a survival of just 40% despite a far more aggressive treatment regimen (Bartlett et al. 2013).

The quality of survival is often not satisfactory; many children are left with cognitive, behavioural and endocrinological sequelae apparently as a result of radiotherapy in combination with chemotherapy and, in some cases, complications of surgery (Grill et al. 2004; Bull et al. 2007; Kennedy et al. 2014) and problems persist into adulthood (Kieffer et al. 2012). These may vary by molecular subtype (Bull et al. 2014b). Medulloblastoma surgery is complicated by cerebellar mutism syndrome (CMS) (see Cognitive and Behavioural Sequelae of Posterior Fossa Surgery in Children section) more frequently than surgery for any other tumour type and is strongly associated with poorer long-term cognitive outcomes. In some cases this is accompanied by persistent ataxia and dysarthria.

CEREBELLAR ASTROCYTOMA

Incidence
Cerebellar astrocytomas are about as frequent as medulloblastomas in children.

Pathobiology of cerebellar astrocytoma
More than 65% of low grade gliomas in childhood are pilocytic astrocytomas although about 20% are diagnosed clinically without biopsy and are therefore presumptive diagnoses. A very small (and unquantified) proportion of pilocytic tumours is thought to transform to more malignant phenotype later in adulthood but risks factors for this have yet to be identified; currently, this is neither quantified nor are there
established predictive factors for this risk. Diffuse/fibrillary astrocytomas account for up to 6%, the remainder being a series of rare entities that do not typically arise in the cerebellum and will be considered with low grade gliomas of the cerebral hemispheres (see Low Grade Glioma of the Cerebral Hemispheres section).

Cerebellar astrocytomas may involve the vermis (particularly in younger children), the hemispheres, or both locations simultaneously. Approximately half are purely midline tumours. About 80% are cystic tumours with a mural nodule attached to one part of the cyst wall (Fig. 14.9). Solid tumours are less common. Metastatic leptomeningeal dissemination occasionally occurs (<10%). The majority are pilocytic astrocytomas that are far more benign than most astrocytomas of later life but exceptional cases of malignant cerebellar astrocytoma are on record as recurrences of operated astrocytomas. Histologically cerebellar astrocytomas can be divided into a juvenile pilocytic form, with microcysts, Rosenthal fibres and oligodendroglial fibres that are slowly growing (WHO Grade I) parenchymal tumours and a less common diffuse type (WHO Grade II) with high cell density necrosis and calcification. The latter type has a less favourable outcome than the juvenile type. The classification of diffuse gliomas is further discussed in the section of this chapter on gliomas of the cerebral hemispheres.

Genetic alterations seen in high-grade gliomas such as TP53 mutation, MGMT methylation, epidermal growth factor receptor amplification, and PTEN loss are not found in juvenile pilocytic astrocytomas and no consistent pattern of loss of heterozygosity on 1p or 19q has been identified or shown an association with outcome (Bonfield and Steinbok 2015). Despite this, several studies have identified an aberration in chromosome 7, the vast majority being a tandem duplication resulting in a KIAA1549: BRAF fusion gene. A smaller number of tumours have other BRAF gene alterations or NF1 mutations. All the genetic mutations seen in this tumour type cause alterations in the MEK/mitogen activated protein kinase (MAPK) pathway, increased transcriptional activity and cellular proliferation, with particular genetic mutations. Pilocytic astrocytoma is therefore considered predominantly a single pathway disease with oncogenic hit distributions that vary with anatomical site (Jones et al. 2012) (Fig. 14.10). However, outcomes do not appear to be influenced by the absence or presence of this alteration. There is also no correlation between the macroscopic appearance of pilocytic astrocytomas and the outcome.

Other genetic associations with low grade glioma in childhood include neurofibromatosis type 2 (NF2) (also associated with acoustic neuroma, multiple spinal ependymoma and peripheral nerve sheath tumours) (see Chapter 4) tuberous sclerosis (see Chapter 4) which presents with subependymal giant cell astrocytoma (SEGA), a benign tumour. Astrocytomas can also present as part of other familial cancer syndromes such as Li Fraumeni Syndrome, constitutional mis-match repair syndrome and familial adenomatous polyposis syndrome (AFP). The Swedish family cancer registry has identified the presentation of low grade glioma in childhood as a marker for nonspecific enhanced family cancer risk (Hemminki and Li 2003).
Clinical features and imaging of cerebellar astrocytoma

The clinical features of cerebellar astrocytomas are similar to those of medulloblastomas but the history is usually much longer and the child less ill so the child often has a prolonged history of symptoms of raised ICP with headaches, vomiting, paralytic squint, ataxia and mobility problems. Papilloedema is frequent because of the long course and slow growth of the tumour and can lead to loss of vision. Delays in diagnosis are common. Occasionally children can die at the time of presentation due to acute hydrocephalus and herniation of cerebellar tonsils. Because tumours may be hemispheric or extend asymmetrically to one hemisphere, unilateral or asymmetrical cerebellar signs are more common than with medulloblastomas. A head tilt away from the lesion is often present.

CT and MRI (Fig. 14.9) usually show large masses, displacing and compressing the fourth ventricle. Low tumour density is mostly due to oedema. On MRI the solid components are typically iso-intense on T1 and hyperintense on T2-weighted images. Contrast injection increases density and can delineate a dense nodule, several pericystic nodules, or a large irregular tumour surrounded by several cysts. Calcification is present in 10–20%. Hydrocephalus of a marked degree is the rule.

Treatment and outlook of cerebellar astrocytoma

Newly diagnosed cases need to be considered by the paediatric neuro-oncology multidisciplinary team. An international consensus has established criteria for case selection for immediate treatment versus observation (Walker et al. 2013). Low grade cerebellar astrocytoma is a surgical disease with excellent long-term results but requiring long-term follow-up. Radiotherapy is not indicated in cases of confirmed complete removal nor in the large majority of cases of incomplete removal but is clearly indicated in the uncommon cases of cerebellar glioblastoma. Late recurrences can be treated surgically. In a single institutional series of 100 children, 9% of the children in this study underwent repeated surgery due to progressive tumour recurrence, and 15% were treated for...
persistent hydrocephalus (Due-Tønnessen et al. 2013). However, in a significant proportion of patients for whom resection is reported as ‘complete’ by the neurosurgeon there was evidence of persistence of tumour tissue by MRI within 3 days of surgery, so postoperative MRI surveillance is essential for early detection of residual disease and subsequent imaging at increasing intervals to screen for the appearance/enlargement of residual tumour. Recurrence (or, more precisely, tumour progression) is much more common after subtotal resection although, even in such cases, it does not necessarily occur and recurrences occasionally regress spontaneously (Palma et al. 2004). Sequelea in groups of survivors include specific cognitive deficits and HRQoL that is significantly lower than that of non-tumour comparison groups although significantly higher than that found in medulloblastoma survivors (Aarsen et al. 2004; Bull et al. 2014).

**EPENDYMOMA**

**INCIDENCE**

Ependymomas are thought to arise from the radial glial cell, a neural stem cell (Taylor et al. 2005) and account for 6–10% of childhood tumours and 15% of posterior fossa tumours. They have a peak incidence in young children. Sixty per cent of cases occur under age of 5 years. Over 90% of ependymomas arise within the cranium, about two-thirds of them below the tentorium. Ependymomas of the fourth ventricle arise from the floor, the roof or the recesses of the cavity and obstruct CSF flow. Ependymomas in the posterior fossa are commonest in very young children, those in the cerebral hemispheres in adolescence and those in the spinal cord in adults. Ependymomas in a supratentorial location are more likely to be malignant; the latter constituting up to 86% of cases in some series. WHO CNS 2016 recognises five types of ependymal tumours: myxopapillary ependymoma (Grade I – usually a spinal tumour), subependymomas (Grade I), ependymoma (Grade II), anaplastic ependymoma (Grade III) and ependymoma, RELA fusion positive (Grade II or III). The last of these accounts for the majority of supratentorial ependymomas in children (Louis et al. 2016).

**PATHOBIOLOGY OF EPENDYMOMA**

The histopathological classification and grading of these tumours remains controversial (Ellison et al. 2008). Anaplastic ependymoma has a poor prognosis compared with its differentiated counterpart and clearly anaplastic and differentiated tumours may be distinguished with a high level of agreement. The histological classification and prognostic significance of the intervening histological spectrum of tumours (e.g. focal anaplasia encountered in a largely differentiated ependymoma; high levels of mitotic activity without vascular proliferation; and vice versa) is less clear (Merchant et al. 2010).

**TREATMENT OF EPENDYMOMA**

Prediction of tumour behaviour has been assisted by molecular subtyping. Chromosomal gains of 1q are commonly associated with ependymoma in children, particularly the intracranial and anaplastic tumour types and genetic imbalances are predictive of tumour site, histological subtype, and age of the patient (Tamburrini et al. 2009; Merchant et al. 2010). Genetic differences in ependymoma may, therefore, be the key to successful risk classification for future clinical trials. The use of messenger RNA profiles in this relatively uncommon tumour type has, however, suggested no fewer than nine ependymoma subgroups (Johnson et al. 2010). Activation of the phosphoinositide 3-kinase (PI3K) pathway, which transduces signals from growth factors and cytokines to alter cell growth, proliferation, and apoptosis, was seen in 72% of 272 ependymoma samples (67% posterior fossa, 22% supratentorial and 6% spinal). That activation was associated with a worse prognosis. The PI3K pathway may, therefore, be a candidate bio-marker to identify patients responsive to therapies targeted against the PI3K pathway (Rogers et al. 2013). It remains unclear to what extent these new discoveries will shape clinical practice.

**CLINICAL FEATURES AND IMAGING OF EPENDYMOMA**

The main clinical manifestations are signs and symptoms of intracranial hypertension and focal deficits. Seizures are relatively uncommon. The clinical manifestations do not permit distinction from other posterior fossa tumours, although palsies of cranial nerves, torticollis and neck stiffness are more common with ependymomas. Imaging showing a midline mass, often filling the fourth ventricle and associated with hydrocephalus. Tumour signal is usually higher than or similar to that of the brain. Cyst formation and calcification are common, often resulting in mixed signal. Enhancement is typically present. Ependymomas may involve the cerebellopontine angle or extend into the cervical spinal canal and frequently metastasise along the CSF pathways. MRI better demonstrates extension of the tumour into the cerebellopontine angle, the cisterna magna and cervical spinal canal, and is important to determine precisely the volume to irradiate. Local recurrence, subarachnoid spread and ventricular seeding can be demonstrated by neuroimaging. In 15% of low-grade and 50% of high-grade infratentorial tumours, meningeal seeding, mainly to the spinal canal, can be detected by gadolinium-enhanced MRI but only rarely by CSF studies. Neuroradiological appearance is nonspecific. Small multiple intratumoural calcification is frequent.
substantially greater percentage than would be expected from population-based incidence—and infratentorial in the other 31%. Tumour histology was Grade II ependymoma in 63%, Grade III anaplastic in 35%, and unknown in 2%. EBRT was both cranial and spinal in 47% and cranial alone in 53% of those who received it. Overall survival rates were higher with infratentorial than with supratentorial tumour location. Progression-free survival rates and time to progression were highest after GTR with supratentorial tumours and after STR + EBRT with infratentorial tumours. This held true both for Grade II and Grade III histology. With Grade II tumours, GTR was the treatment with the highest overall survival rate while for Grade III tumours, in contrast, highest survival rates followed STR + EBRT (Cage et al. 2013).

Gross total excision is often technically very difficult as tumours may be adherent to the floor of the fourth ventricle or cerebellar peduncle, encompass cranial nerves and arteries in the cerebellopontine angle, invaginate the brainstem or surround the basilar artery and brainstem perforators. Complete resection is therefore often not possible but it results in the highest rates of event-free and overall survival. Several reports have concluded that the most important prognostic factor is complete resection, achievable in a higher proportion of supratentorial tumours, and, to a lesser extent, the use of radiotherapy (Van Veelen-Vincent et al. 2002; Grill et al. 2003; Merchant et al. 2004; Massimino et al. 2004; Merchant et al. 2013). The morbidity of aggressive surgery can include deafness and bulbar problems. Many surgeons consider accepting this significant morbidity in order to achieve gross total excision with its associated better survival rate.

Chemotherapy has no proven efficacy (Van Veelen-Vincent et al. 2002; Massimino et al. 2004; Merchant et al. 2004) and has had no impact on the incidence of local recurrences, which are the major threat. It may, however, be used to try to delay radiotherapy to beyond 3 years of age or to reduce tumour vascularity and thus increase the chance of complete resection.

Local irradiation has been clearly shown to improve survival rates and is associated with the highest survival rates when used immediately after surgery (Merchant et al. 2009a). New irradiation techniques, especially conformational, intensity modulated radiotherapy improve the tolerability of this treatment (Merchant 2002). The advent of conformal radiation therapy coincided with improved neuroimaging, neurosurgical navigation, and the systematic use of second surgery before irradiation for patients initially treated with incomplete resection. More effective surgery combined with high-dose postoperative radiation therapy increased local tumour control rates and event-free survival, shifting the pattern of failure from predominantly local to similar numbers of local and distant failures. Long-term sequelae following such treatments in specialist centres have been favourably reviewed (Merchant et al. 2010) and conformal therapy is now part of the first-line management of children regardless of age. Most treatment failures are related to local recurrences with or without spinal recurrence and isolated spinal recurrence is extremely rare. The need for spinal irradiation currently is therefore not generally accepted and is only indicated in malignant posterior fossa tumours with metastatic spread. The advantages of proton beam therapy (discussed in the Treatment: General Considerations section) are particularly pertinent to treatment of ependymomas that require high doses of local radiotherapy and are usually immediately adjacent to critical neural structures.

In summary, treatment includes as complete as possible resection, followed by radiotherapy in children over the age of 3 or 5 years, depending upon local practice criteria. Recurrent tumour is managed with repeat surgical resection if feasible and sometimes by repeat irradiation.

Outlook of ependymoma

The prognosis remains guarded (Packer 2005). The small numbers of cases subdivided between age, location, histopathology, molecular subtype, degree of resection and stage have led to conflicting reports regarding prognostic factors (Tamburrini et al. 2009; Cage et al. 2013). A young age is the most important negative prognostic factor. Reported rates of 5-year survival vary widely from 24% to 82% (Rogers et al. 2013) but survival rates after complete resection have been reported to be as high as 90% (Van Veelen-Vincent et al. 2002). Although survival rates are reported to be poorer for children under 2–3 years, this may simply reflect the fact that a higher proportion of the youngest children have tumours in which complete resection is not achieved. Considering all intracranial ependymomas diagnosed at age 0–19 years in the US SEER registry from 1973 to 2011, 5-year survival was 85% and 30-year overall survival and cancer-specific survival of those in this age range that were in follow up having survived the first 5 years from diagnosis, were 57.3% and 68.6% respectively (Frandsen et al. 2015).

Other Tumours of the Cerebellum and IVth Ventricle

Subependymomas are rare in children. They are variously interpreted as hamartomaticous growths of subependymal cells, or growths of astrocytes or oligoglia. These tumours grow extremely slowly and are often discovered fortuitously, for example at post-mortem examination. Most are located in the floor of the fourth ventricle. They may occasionally be symptomatic and then have a good prognosis. They may also occur supratentorially particularly in the lateral ventricle.

Cerebellar haemangioblastomas are rare in childhood. Approximately a quarter of the cases are an expression of the von Hippel–Lindau disease. In such cases the tumour may be discovered at a preclinical stage. Angiography visualises the solid part of these tumours, most of which are cystic with a single mural nodule. CT visualises the cysts, but visualisation of the nodule may be possible only after enhancement.
Solid tumours are rare and mimic meningiomas. MRI with or without gadolinium enhancement gives a characteristic picture with a ring of increased signal surrounding the tumoural cyst. The prognosis following resection is favourable for cystic tumours.

**Cerebellar sarcomas** are usually located to one cerebellar hemisphere (Oliveira et al. 2002). They run a rapid and severe course. On CT they present as areas of spontaneously increased density with ill-defined limits that become denser after contrast injection.

**Schwannomas of the VIIIth nerve** are rare in children. They may be unilateral or bilateral. In the latter case, they are usually a component of type 2 neurofibromatosis (Chapter 4). They can be responsible for deafness, often associated with facial paralysis and a contralateral cerebellar syndrome (Verstappen et al. 2005). The diagnosis rests on radiological demonstration of the tumour, which is most effectively visualised by MRI. They may be multiple and may involve the 8th nerve.

Other rare tumours of the cerebellopontine angle include epidermoid cysts and meningiomas. Approximately 30% of posterior fossa meningiomas in children show aggressive characteristics.

**Arachnoid cysts** are considered in the Arachnoid Cysts section at the end of this chapter.

**Dermoid cysts** of the posterior fossa are generally midline tumours. They are often associated with a cutaneous fistula piercing the occipital squama. They rarely behave as tumours and are more commonly revealed by meningitis. They may be associated with cervical spinal abnormalities including Klippel–Feil malformation (Muzumdar and Goel 2001). Removal of the cyst and tract is the effective treatment (Caldarelli et al. 2004).

**Gangliocytoma of the cerebellum** (Lhermitte–Duclos disease) presents as a diffuse increase in volume of several cerebellar lamellae, usually with a predominance on one cerebellar hemisphere. There is diffuse hypertrophy of both the white and grey matter. MRI gives highly suggestive images of localised lamellar hypertrophy with increased signal on T2-weighted sequences (Nagaraja et al. 2004). Lhermitte–Duclos disease is a feature of the Cowden syndrome of multiple hamartomas in at least one-third of cases. Pérez-Núñez et al. (2004) found asymptomatic cases by systematically studying cases of Cowden syndrome seen in a dermatological unit. Cowden syndrome is associated with mutations in the PTEN gene. This gene is also implicated in other hamartomatous syndromes such as Proteus syndrome and activation of the AKT/mTOR pathway (Abel et al. 2005).

**Cognitive and Behavioural Sequelae of Posterior Fossa Surgery in Children**

Complications of surgery for posterior fossa tumours are common. The presence of hydrocephalus or its development postoperatively is very common and may require endoscopic IIIrd ventriculostomy or shunting. Management of hydrocephalus with an endoscopic IIIrd ventriculostomy prior to tumour removal reduces the incidence of post-resection hydrocephalus (Di Rocco et al. 2013). The occurrence of cognitive, affective and behavioural problems has been recognised only in recent decades. The most striking manifestation is the so-called cerebellar mutism syndrome (CMS). This was originally described in 1984 (Wisoff and Epstein 1984), although the term itself was coined later. CMS was reported with increased frequency in the late 1990s and early 2000s in association with more aggressive surgery to resect posterior fossa tumours, most commonly medulloblastoma. It has been reported to affect 24% of children with medulloblastoma (Robertson et al. 2006) although some centres recognise it in only 5–10% of cases. It is characterised by development of mutism, or more precisely anarthria, in the peri-operative period, often associated with severe distress and transient personality change, emotional lability, decreased initiation of voluntary movements, impaired swallowing, ataxia, weakness and hypotonia. Like the cerebellar cognitive affective syndrome described in adults (Schmahmann and Sherman 1998), mutism arises in association with damage to the vermis but the precise cause of CMS remains unclear.

Mutism may start within hours of surgery but onset has been reported as long as 9 days post-surgery. It lasts from 1 to 20 weeks. Although the mutism is transient, patients affected by it also have more significant neurological and cognitive deficits at 1 year and more cerebellar atrophy in proportion to the severity of the CMS (Wells et al. 2008, 2010). Dysarthria and ataxia may remain present for years and there is a clear association between postoperative mutism and subsequent cognitive impairment (Wells et al. 2008; Câmara-Costa et al. 2015). Rare cases of this syndrome have been reported following non-surgical insults (haemolytic–uraemic syndrome and cerebellitis) (Mwasingih et al. 2003). Reviews have identified associations between CMS and large tumours, pre-operative pontine compression, excessive para-vermian manipulation, damage to the dentate nuclei pathways, and lesions in some supratentorial structures. Ersahin et al. (2002) demonstrated by SPECT the presence of reversible circulatory disturbances. Recent studies have focused on abnormalities in efferent cerebellar pathways including the dentato-thalamo-cortical outflow tracts, detectable on diffusion tensor MRI (Morris et al. 2009; Avula et al. 2015). Bilateral surgical damage to the proximal efferent cerebellar pathways is strongly associated with CMS and it has been suggested that bilateral hypertrophic olivary degeneration after posterior fossa surgery may be a sensitive and, in appropriate clinical settings, reliable MRI indicator of bilateral disruption of the proximal efferent cerebellar pathways and consequently of CMS (Patay 2015). A standardised rating scale is needed to improve identification of the syndrome, risk factors for its occurrence, and means to prevent and treat it.

Resection of posterior fossa tumours is also associated with other cognitive or behavioural difficulties. Rønning et al. (2005) reported on persistent cognitive problems in young
adults following posterior fossa surgery. Steinlin et al. (2003) found decreased verbal fluency in 24 children operated on for benign tumours (low grade cerebellar astrocytomas) in addition to subtle abnormalities in subtests despite normal global IQs. Richter et al. (2005a) described behavioural–cognitive changes in children and adolescents with chronic cerebellar lesions and studied prospectively the incidence of dysarthria following complete resection of cerebellar tumours (Richter et al. 2005b). Konczak et al. (2005) reported that working memory was impaired in those children and adolescents that had chemo- or radiotherapy in addition to posterior fossa tumour surgery. Disturbances of equilibrium and fine motor skills were found in two-thirds of patients. Bull et al. (2014a) reported deficits compared to a non-tumour comparison group in 72 children aged 8–14 years treated for cerebellar tumours with respect to IQ, executive and behavioural function, health status and quality of life. These deficits were greater following adjuvant therapy with chemo- or radiotherapy for medulloblastoma than following surgery alone for low grade gliomas. Such difficulties confirm the importance of the cerebellum in several non-motor skills as expected on the basis of neuro-anatomical studies (Levisohn et al. 2000; Schmahmann 2010).

**BRAINSTEM TUMOURS**

**Incidence**

Tumours of the brainstem account for 5–11% of all intracranial tumours in childhood and for 13–29% of infratentorial tumours (Ostrom et al. 2014). The peak incidence of diffuse midline gliomas is between 5 and 9 years of age.

**Pathobiology of brainstem tumours**

Pilocytic astrocytoma, diffuse midline glioma, H3 K27M-mutant (previously known as diffuse intrinsic pontine glioma) and glioblastoma are the three main histological types in series verified at autopsy or by biopsy. The histological and genetic basis of this classification is further discussed in the Gliomas of the Cerebral Hemispheres section. Histological and anatomical discrimination is critical for prognostication, as low grade glioma of the brainstem can be expected to respond to surgical decompression or debulking and may respond to chemotherapy or radiotherapy. In NF1, brainstem (and cerebellar) tumours are also seen but are generally non-progressive. NF1 associated tumours, which have the capacity for progressive enlargement, particularly affect brainstem (and/or visual pathways considered later in this chapter) and must be distinguished on cranial imaging from non-progressive focal areas of signal intensity (FASI) and neurofibromatous bright objects (NBOs). FASI are iso-intense on T1-weighted images and hyperintense on T2/FLAIR images and frequently affect the cerebellar hemispheres and basal ganglia. NBOs are focal, well-defined areas of high signal change on T2-weighted sequences found in the basal ganglia, brainstem, cerebellum, and occasionally in the subcortical white matter and dentate nuclei. NBOs are reported to proliferate during childhood and involute during adolescence and early adulthood.

Pilocytic astrocytomas tend to occur in the dorsal medulla or cranio-cervical junction and to become dorsally exophytic, growing into the fourth ventricle or the brainstem cisterns, whereas diffuse midline gliomas involve mainly the ventral pons engulfing the basilar artery and producing a diffuse increase in the size of the brainstem while remaining entirely contained within the brainstem parenchyma. A third group is formed by tumours of the tectal plate and peduncles and a fourth group includes tumours involving the medullospinal junction. Meningeal seeding, especially spinal, is not rare. Brainstem tumours are in fact a histologically heterogeneous group that includes cases with different clinical and imaging presentations and, especially, different prognoses and treatments (Jallo et al. 2004). Other variations include diffuse astrocytomas and rare cases of xanto-astrocytomas, which despite the presence of increased cellularity, pleomorphism and necrosis behave in a benign fashion.

**Clinical features and imaging of brainstem tumours**

The history is usually short in the case of diffuse midline tumours. The clinical presentation is usually with multiple palsies of the VIIth to XIIth cranial nerves and ocular motor palsies. The classic clinical presentation is with a combination of ataxia, cranial nerve palsies and long tract signs. These features typically start unilaterally and eventually become bilateral. Symptoms of increased ICP usually appear late, and papilloedema is often absent. However, vomiting, unassociated with evidence of increased ICP, is often present, probably as a result of direct involvement of brainstem centres. Irritability and emotional instability are common. Paroxysmal facial or nuchal itching may be the presenting sign.

Dorsal exophytic gliomas developing posteriorly into the fourth ventricle can produce obstructive hydrocephalus. Tumours of the quadrigeminal plate (Daglioglu et al. 2003) and periaqueductal tumours (pencil tumours) usually present with hydrocephalus or with ocular motor signs, classically with Parinaud syndrome (loss of pupillary reaction to light, loss of voluntary vertical gaze, and eyelid retraction). MRI examination has shown these tumours to be a common cause of aqueductal stenosis. They are usually very slow growing or remain static for long periods, so no primary treatment is required beyond CSF shunting. Such lesions commonly occur with NF1. Brainstem hamartomas are frequent in this disease, usually involve the medulla and are commonly static or slow growing and occasionally regress spontaneously. CSF diversion is sometimes required and careful surveillance is prudent but more aggressive treatment is rarely needed.

Tumours of the cervicomedullary junction commonly originate in the upper spinal cord and grow upwards, or have a bulbar onset and a downward course. They manifest with
involvement of the lower cranial nerves. Clinical features may include dysphonia, dysphagia, abnormal breathing, vomiting or quadriplegia. Atypical presentations include failure to thrive, acute hemiplegia, a syndrome of the cerebellor pontine angle, intractable vomiting and psychiatric symptoms.

The diagnosis of brainstem tumour rests on imaging. CT showing an increase in the anteroposterior diameter of the brainstem with posterior displacement and compression of the fourth ventricle and of the interpeduncular and peripontine cisterns. The lateral and third ventricles are dilated in a quarter of the cases. In most cases, the density of the brainstem parenchyma is altered. Isodense tumours may appear only with enhancement. Hypodense lesions and ring enhancement are associated with a poor outlook and are mainly associated with higher grade gliomas. Exophytic and dorsal expansion of the tumour, calcification and cysts are associated with lower grade astrocytomas and a better outlook. MRI (Fig. 14.11) gives a precise indication of the vertical extent of the tumour, better defines exophytic components and their relationship to neighbouring structures and allows a clear distinction between focal and diffuse gliomas.

Although tumour biopsy is not necessary for the diagnosis of diffuse midline glioma with typical radiological and clinical features, the case for obtaining additional information at biopsy becomes increasingly strong as better understanding of the molecular pathways of tumorigenesis brings biologically driven new therapies closer to clinical practice.

The differential diagnosis of brainstem neoplasms may be difficult. It includes brainstem encephalitis that may give rise to swelling of the stem and changes in density or signal, multiple sclerosis, haematomas or vascular malformations, parasitic cysts and tuberculomas. The last of these should always be considered, especially in patients from resource poor settings or with increased genetic susceptibility to mycobacteria. Behçet disease has been responsible for midbrain mass. Other mass lesions of that region such as enterogenic cysts or epidermoid cysts are exceptional and their images are very different from those of gliomas.

**Treatment of Brainstem Tumours**

Treatment of hydrocephalus with third ventriculostomy or ventriculo-peritoneal shunt may be required. The treatment of brainstem gliomas otherwise depends totally on the type of tumour. In the most common diffuse midline glioma, radiotherapy is often associated with short term remission from symptoms that then reappear and progress inexorably usually after an interval of 6–12 months. These tumours are sometimes surprisingly radiosensitive with dramatic resolution of imaging abnormalities after initial radiotherapy-induced swelling (‘pseudoprogression’) which may be mitigated with steroid therapy. Systemic chemotherapy has not been shown to be of benefit for this tumour type (Hargrave et al. 2006; Khatua et al. 2011).

For focal tumours, surgery, if necessary augmented by chemotherapy or, if this is not effective, irradiation, can be an effective tool. Biopsy is usually necessary to establish a diagnosis and rule out other rare diagnoses with therapeutic implications. Surgical resection of focal tumours, including exophytic tumours and those of the cervicomedullary

![Figure 14.11 Malignant midline glioma of the brainstem.](image-url)
junction, is indicated. These are usually benign, slow-growing tumours. Drainage of cysts associated with tumour may be of great therapeutic benefit.

**OUTLOOK OF BRAINSTEM TUMOURS**

The outcome is correlated with the type, with diffuse gliomas having a younger age at onset and a much worse prognosis (Fisher et al. 2000). Diffuse midline glioma is not radio-curable and the median survival time following diagnosis is 10 months with very few children surviving for 2 years. Longer survival times are seen in a small minority of cases and probably relate to different types of glioma. By contrast, radical excision of focal low grade exophytic or cervicomedullary gliomas is sometimes possible, in spite of surgically uninviting appearance on imaging, and has been reported to give up to 100% survival rate.

**TUMOURS OF THE MIDLINE AND BASE OF THE BRAIN**

Several pathologically diverse tumours arise from the midline region of the brain or from nearby structures such as cranial nerves, hypophysis, epiphysis and residua of the notochord. Craniopharyngioma is the most common midline tumour, followed by optic pathway tumours. Most midline tumours may produce, visual impairment, endocrine and metabolic abnormalities, and increased ICP through the development of hydrocephalus.

**CRANIOPHARYNGIOMA**

**INCIDENCE**

Craniopharyngiomas represent about 50% of midline tumours and 4–9% of all tumours in infancy and childhood.

**PATHOBIOLOGY OF CRANIOPHARYNGIOMA**

They arise from small cellular rests that are considered to represent remnants of the embryonic Rathke pouch and may develop either in the suprasellar region or in both suprasellar and infrasellar regions. Purely infrasellar craniopharyngiomas are rare in children. Most craniopharyngiomas are partly or completely cystic. The microscopic appearance is variable with squamous epithelium that may be thickened or degenerate with formation of microcysts. Calcification is a frequent and important feature of craniopharyngiomas. Craniopharyngiomas may manifest at any age from the neonatal period to adulthood.

**CLINICAL FEATURES AND IMAGING OF CRANIOPHARYNGIOMA**

The clinical features of craniopharyngioma are the result of endocrine abnormalities, interference of the tumour with neighbouring structures, especially the optic pathways and increased ICP secondary to hydrocephalus. Delayed growth resulting from growth hormone deficiency is a common and often the first feature, although it is often found only in retrospect and may be absent in about half the cases. Weight gain due to hypothalamic disturbance may pre-date surgery. Excess weight gain, fatiguability and declining school performance are common and may be associated with hypothyroidism. Diabetes insipidus results in excessive thirst and frequent urination. Less commonly, disturbances in fluid and electrolyte balance or abnormalities of autonomic function are present.

Visual disturbances and symptoms and signs of increased pressure are present at the time of diagnosis in a majority of patients and indeed are the most frequent initial manifestation in children. They include visual complaints, subtle alteration of alertness and conscious level, vomiting, bitemporal hemianopia, nystagmus and optic atrophy. Papilloedema is less common. Ataxia is occasionally observed, wrongly suggesting the diagnosis of a posterior fossa tumour. Somnolence, apathy and change of mood are not infrequently present including in patients without increased pressure. Unilateral loss of vision may supervene rapidly, mimicking optic neuritis. Focal neurological signs are uncommon.

Skull X-rays regularly demonstrate erosion of the dorsum sellae or enlargement of the sella turcica or both. Imaging (Fig. 14.12) showing, in most cases, a cystic lesion that is suprasellar or intra- and suprasellar. The suprasellar expansion may be quite large, compressing the third ventricle and reaching the septum pellucidum or even the corpus callosum. Retrosellar expansions are less frequent. The density of the tumour before contrast injection is heterogeneous. Calcification is present in 80% of cases. In rare cases, the tumour may be difficult to visualise or have an unusually dense appearance and extension. MRI is more precise than CT and medial sagittal views are particularly valuable for defining the relationship of the tumour to the optic nerve, chiasm, hypothalamus and brainstem, for the detection of small tumour remnants after surgery, and for exploration of the content of the sella turcica, which is difficult to assess by CT because of the presence of bone artefacts.

Endocrinological studies reveal a deficiency of growth hormone pre-dating surgery in approximately half the patients. Gonadotropic hormones are also low in about 50% of pubertal patients. Diabetes insipidus and deficits in thyrotropin (TSH) and adrenocorticotropic (ACTH) are less common in non-operated patients but appear in most patients following surgery.

The diagnosis of craniopharyngioma is often not made until a surprisingly long period of symptoms has passed. Acute presentation, young age and visual deficits at presentation are clinical features with an adverse prognosis. Once the diagnosis is suspected, other tumours of the region should be excluded. Rarely, a craniopharyngioma may produce the diencephalic cachexia syndrome.
Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri

Chapter 14

Treatment of Craniopharyngioma

Surgical treatment is generally advised. Surgery combined with postoperative radiotherapy is the commonest protocol. The extent of surgery remains controversial. In general the goals of surgery are to decompress significant cysts and then to remove as much tumour below the hypothalamus as possible. Decompression of cysts can be achieved by open approaches, via a trans-ventricular endoscopic approach or via a stereotactic approach. For the suprachiasmatic and the subchiasmatic solid components there are a variety of approaches and techniques available including an extended endoscopic endo-nasal approach, interhemispheric approach, subfrontal approach, cerebellopontine angle approach, translamin a terminalis approach and a transsylvian approach. The appropriate approach depends on the location of the tumour. It is generally accepted that tumour adherent to the hypothalamus should not be removed. A number of procedures may be required prior to the second stage of treatment with radiotherapy. Attempts to avoid the many problems seen postoperatively (see following paragraphs) have led to a search for different therapeutic methods, including radiosurgery (Kobayashi et al. 2005), neuro-endoscopic surgery (Delitala et al. 2004), intracystic chemotherapy with bleomycin (Mottolese et al. 2001, 2005), and intracystic irradiation with radioactive agents. It is not currently possible to assess these methods fully but they may be of value in some cases.

In most cases, partial excision combined with postoperative irradiation results in a dramatic reduction of the recurrence rate from 75% to 30%, and is generally advised. It can be given as classic radiotherapy, or as proton beam radiotherapy or with stereotactic methods (Kobayashi et al. 2005). With either partial or total resection, the mortality rate has considerably decreased and survival rates are now high (Muller et al. 2004a; Poretti et al. 2004; Stripp et al. 2004). Recurrence rates differ in different studies but do not seem to be grossly higher after partial excision than those obtained with attempted ‘complete’ removal. In a large series of 121 craniopharyngiomas in children and adults, 23% with a suprasellar component, complete removal was achieved in 16 patients and partial removal in 84, while other techniques were employed in other patients including cyst drainage or removal. Radiotherapy was used in about a third of the patients. Survival rates were best in cases of compete removal but were generally high in all (Karavitaki et al. 2005).

Outlook of Craniopharyngioma

The major consideration in the management of craniopharyngioma is now more the quality of survival following treatment.
rather than survival. The avoidance of damage to the hypothalamus is important to the achievement of this end. Complete removal and radiotherapy are fraught with many dangers. They may produce deafness, lowering of IQ levels, endocrinological disturbances and even neurological sequelae. For young children with only partial resection, it may be best to delay irradiation as much as possible because of the greater severity of unwanted effects of irradiation in that age group.

Panhypopituitarism is common postoperatively and poses therapeutic, sometimes life-threatening, problems that require special attention (Theodosopoulos et al. 2012). Diabetes insipidus develops in three-quarters and deficiency of TSH and ACTH of the patients in one-quarter of the patients. ADH deficiency in 9–34% may be masked until ACTH deficiency is corrected. However, a paradoxical growth spurt following surgery has been reported.

Growth retardation can be treated with growth hormone with reasonable success (Muller et al. 2004b). The development of gross obesity in some children, often associated with behavioural problems and loss of neuro-vegetative homeostasis, raises major practical problems and may represent a cardiac threat (Lustig et al. 2003). Unlike endocrinological disturbance, it is not amenable to treatment and seems to be due to surgical injury to the hypothalamus. Prediction of these complications is difficult (Hayward et al. 2004). The current trend, therefore, is to leave some tumour tissue rather than taking these risks.

A variety of neurocognitive deficits are often associated. Epilepsy is present in around 10% of patients and may be intractable medically, especially when of frontal lobe origin, and require surgical treatment. The role of focal radiotherapy in causing epilepsy and in determining IQ in this group of patients with complex problems is debated but newer techniques for delivering radiotherapy to a field with sharply defined margins sparing adjacent neural tissue, discussed in earlier parts of this chapter, offers the promise of reduced morbidity. A long-running longitudinal follow-up study of 261 patients diagnosed before 2000 with childhood-onset craniopharyngioma reports that 20-year overall survival was 84% and 95% in those with and without hypothalamic involvement respectively and that this was not related to degree of resection, sex, age at diagnosis, or year of diagnosis. Progression-free survival was 39%, 52% and 77% in patients aged less than 5 years, 5–10 years and more than 10 years at diagnosis respectively. Hypothalamic involvement led to severe weight gain (+4.59 standard deviations) in the first 8–12 years (with no subsequent further increase) and to impairment of quality of life by obesity, physical fatigue, reduced motivation, dyspnea, diarrhoea and nonoptimal psychosocial development (Sterkenburg et al. 2015).

In summary, the management is complex and controversial and the need for a multidisciplinary approach including all relevant disciplines and with the necessary priority being accorded to quality of survival, essential to the management of all intracranial childhood tumours, is paramount (Hayward et al. 2004).

VISUAL PATHWAY AND HYPOTHALAMIC TUMOURS

INCIDENCE

Visual pathway tumours represent 3–5% of primary intracranial neoplasms in children. A large majority of these are gliomas. Other entities such as nerve sheath tumours, meningioma, and oligodendroglioma and other Grade II tumours of optic radiation are rare in childhood but do occur. Historically these have been appropriately referred to as visual pathway tumours until tissue diagnosis is made. Increasingly, however, biopsy is considered a prerequisite for active management, even in NF1 and/or with characteristic imaging appearances, because molecular genetics is increasingly likely to influence the decision whether to observe or treat and the choice of chemotherapeutic agent. The section below relates to visual pathway gliomas (VPG) only. Ninety per cent of VPGs occur in children.

Approximately 26–36% of VPGs involve the prechiasmatic portion (optic nerves) and 64–74% involve the chiasm and tracts with or without involvement of the anterior third ventricle. NF1 is present in 10–15% of symptomatic pilocytic astrocytomas and this tumour type affects up to 20% of those diagnosed with NF1 in childhood. These are key observations.

PATHOBILOGY OF VISUAL PATHWAY GLIOMAS

Visual pathway gliomas (VPGs) are typical pilocytic astrocytomas consisting of compact fibrillar areas with Rosenthal fibres and looser areas characterised by microcysts, or mixed astrocytomas and oligodendrogliomas. Malignant changes are rare. Molecular biological aspects were considered above, in the account of low grade gliomas of the cerebellum and brainstem.

CLINICAL FEATURES OF VISUAL PATHWAY GLIOMAS

The clinical presentation of VPGs depends on the anatomical location of the lesion. Anterior lesions, confined to the optic nerve anterior to the chiasm, usually present with proptosis, which is often a late sign and monocular visual loss developing over 6–12 months. This may easily be missed in children who adjust to gradual loss of vision. Papilloedema or optic atrophy are present on fundus examination.

In children with posterior lesions involving the optic chiasm or extending further back along the optic radiations, loss of visual acuity is the common presentation. It is often asymmetrical or even unilateral, and in infants aged less than 2 years, may be accompanied by an acquired pendular nystagmus that should not be mistaken for congenital nystagmus. Rarely monocular nystagmus mimicking spasmus nutans may be seen. Sudden visual loss simulating optic neuritis may occur. Visual field loss is variable. A symmetrical bitemporal hemianopia is less common than irregular, asymmetrical field defects or a central scotoma with contralateral impairment of the visual field. Fundoscopic examination generally
showing optic atrophy, although papilloedema is occasionally noted. Papilloedema and nystagmus suggest chiasmatic involvement, whereas blurred discs with visual loss suggest an intraorbital lesion.

With large lesions, there may be compression of the third ventricle with hydrocephalus, and involvement of the hypothalamus may give rise to precocious puberty, diabetes insipidus or obesity or, rarely, to diencephalic cachexia.

Midline location supratentorial tumours typically have clinical features of hypothalamic disturbance, visual symptoms and signs and symptoms of raised ICP. A significant proportion present in infancy and early childhood with the classic features of hypermetabolic diencephalic syndrome (Kilday et al. 2014) of Russell. This is not limited to gliomas of the floor of the third ventricle and is common with optic gliomas and occasionally encountered with craniopharyngiomas and posterior fossa tumours. Conversely, other manifestations such as obesity, diabetes insipidus, hypogonadism and hydrocephalus are frequently encountered. This presentation is often associated with hypopituitarism, signs of accelerated head growth and visual signs or symptoms such as dysconjugate eye movements or nystagmus. The clinical feature of failure to thrive may predominate and indicate the need for brain scanning (Fig. 14.13). In this early age presentation, the tumours can be very large, occupying a significant proportion of the supra-tentorial compartment. When chiasmatic pilocytic tumours present later in life, the tumours are smaller but can still cause significant neurological and endocrine problems and continue to grow.

Hypothalamic tumours predominantly present in the first 5 years and tend to stabilise and stop growing after age 5 years, although there are exceptions.

**NF1 and Visual Pathway Gliomas**

In cases associated with NF1, tumours can involve one or many sectors of the visual pathways from optic nerves, presenting, with proptosis and optic atrophy, to the chiasm and optic radiations. A study of 84 VPGs in NF1 reported that involvement was confined to the anterior visual pathway in
27% (including 5% with bilateral involvement), to the chiasm only in a further 27%, to one or both optic nerves plus the optic chiasm in 30%, and to chiasm and optic radiations in 6%. The remaining 10% had combined involvement of anterior visual pathway, chiasm and optic radiation (Guillamo et al. 2003). Screening systematically all patients with neurofibromatosis for optic gliomas would probably increase the apparent frequency of these tumours. However, current recommendations based on symptomatic tumours may not be applicable to gliomas discovered by systematic investigation in patients with neurofibromatosis. Therefore, screening is not recommended.

**Imaging of Visual Pathway Gliomas**

Imaging, especially MRI, is of primary importance for the diagnosis of VPGs. High-resolution CT can detect even small tumours in the orbit but is less effective than MRI for assessment of intracranial extensions of optic gliomas (Fig. 14.14). The density of chiasmatic tumours is close to that of the cerebral tissue, and homogeneous enhancement is usually obtained following injection of contrast. Tumoural cysts and calcification may be present. MRI visualises small intracranial tumours extremely well, and multiplanar views are valuable to that effect. Intraorbital gliomas are readily identified on frontal cuts, and it has been reported that MRI identifies perineural arachnoidal gliomatosis characterised by a fusiform area of high signal intensity with a central core of lower intensity in patients with neurofibromatosis. Visual evoked potentials are apt to be more abnormal in patients with chiasmatic gliomas than in those with more anteriorly located tumours and visual evoked potentials may be used to follow up the course of optic gliomas (Trisciuzzi et al. 2004). False positives are, however, common, limiting the usefulness of the technique.

**Treatment of Visual Pathway Gliomas**

The review of the surgical management of these tumours which can be found in the chapter by O’Kelly and Rutka (2008) is recommended. Where surgical resection is not feasible and if the tumour is causing severe symptoms or is progressive and threatens neurological function, primary chemotherapy is currently recommended. The commonest reason for considering non-surgical therapy for low grade glioma is in VPG, where saving vision in the young children who present is a serious concern for parents.

**The history of evaluations of chemotherapy in low grade glioma**

Historically, radiotherapy was used leading in many cases to severe neurotoxicity, affecting the child’s subsequent growth, endocrine and cognitive development and the risk of second tumours (Fouladi et al. 2003a). The introduction of chemotherapy in the 1980s was shown to successfully control tumour progression in very young children with progressive, unresectable tumours. Vincristine and Actinomycin D were used initially. A series of phase 2 trials identified a range of chemotherapy agents with comparable activity when given alone, or in combinations. Where radiotherapy had been used it had produced both symptomatic and imaging responses, saving vision in a significant proportion of cases. Where chemotherapy was used, drug resistance did not seem to occur.

Drug selection was driven by seeking to avoid drugs with unacceptable toxicity; for example, cisplatin-induced hearing loss, high cumulative doses of alkylating agents – such as cyclophosphamide, etoposide, CCNU and procarbazine, or genotoxicity, particularly in NF1 – a cancer predisposition syndrome. The most widely used combination of drugs has been vincristine and carboplatin.

Two randomised treatment trials have been reported. A trial of two versus four drugs (vincristine and carboplatin – VCP versus thioguanine, procarbazine, CCNU and vinblastine – TPCV), given over a 12-month period to all post-biopsy patients regardless of their disease progression status, was undertaken by the US Children’s Oncology Group (COG) in USA (Ater et al. 2012). The VCP arm and the TPCV arm included one and three potentially genotoxic drugs, respectively. Allocation to TPCV, not in regular use as a primary treatment, was associated with a superior progression-free survival at 12 months. A European SIOP-E trial found no inter-arm difference in progression-free survival rates associated with random allocation to the addition (or not) of etoposide to a standard VCP induction regimen of chemotherapy (Gnekow et al. 2017).

The experience of these trials has highlighted the need to study children with and without NF1 separately, the need for new targeted agents in those who demonstrate early progression,
and the need to measure vision and neurological symptoms as specific outcome measures in future trials.

The combination of vincristine and carboplatin remains the first-line treatment for newly diagnosed patients with low-grade glioma with progressive disease or at risk of symptomatic disease. Exploring the use of less toxic chemotherapy with fewer side effects in low risk patients; for example, NF1-associated tumours, is a priority in this benign and self-limiting condition. Late or sustained progression after stopping treatment, particularly in younger children with hypothalamic chiasmal tumours, sometimes requires multiple phases of therapy, including radiotherapy and occasionally surgical resection. Selecting cases for observation versus immediate treatment remains a challenge, a consensus is emerging where immediate treatment is recommended in children when clinical or radiological evaluation suggests that the tumour threatens vision bilaterally there is a history of visual deterioration, or the child is very young so that visual testing is limited (Taylor et al. 2008). Symptomatic proptosis is also an indication for medical therapy if there is the possibility of retaining or saving vision.

Conventional conformal (photon) radiation therapy has a useful role in older children who do not have neurofibromatosis, especially for the treatment of bilateral tumours and chiasmal gliomas (Merchant et al. 2009b) and proton beam therapy has also been used in this situation. Reduction in size of the tumour and improvement in vision undoubtedly occur.

Outlook of visual pathway gliomas

The combination of cisplatin and vincristine, applied according to standardised selection criteria, is associated with 5-year overall survival rates greater than 85% and 80% rate of stabilisation of symptomatic progressive disease in international studies that included Grade I pilocytic astrocytoma in 60% and Grade II diffuse astrocytoma in 40%. The latter group had poorer progression-free survival with the same treatment (Stokland et al. 2010; Gnekow et al. 2012). Progressive disease was seen in up to 30% of cases, predominantly children under 1 year at diagnosis with diencephalic syndrome and hypothalamic tumours. VPGs and other low grade gliomas associated with NF1 had a more favourable prognosis for progression-free and overall survival.

With this experience of chemotherapy responses and the experience of radiation neuro-toxicity, the decision to use radiotherapy is now usually deferred until chemotherapy and surgery has been seen to fail. We can expect 90% non-progression rates at 6 months in children presenting with newly diagnosed VPG. Their natural history is for the most part slow. They are often diagnosed early but tend to remain static in many cases and occasionally regress. However, they are tumours rather than hamartomas and some, particularly in children under the age of 8 years, may have a rapid evolution that is difficult to predict. In general the risk of tumour progression is greatest during the first 3–5 years of life.

In children diagnosed with NF1, surveillance programmes of visual function are in place to identify children with visual changes justifying brain imaging to look for VPGs and screening with imaging is used in some countries (Simmons and Gogi 2010). There is uncertainty surrounding methods for early detection that compound uncertainties surrounding the criteria for selecting patients for observation versus treatment (Opocher et al. 2006; Campagna et al. 2010) as well as the efficacy of treatments to save vision. Furthermore there is an established lack of correlation between changes in imaging appearances and visual function. These factors highlight the need for new, well-designed clinical trials focused upon the impact of treatments for patients at greatest risk of visual loss with new treatments directed at saving vision. The mechanism of nerve injury in NF1 needs to be described so as to help select more effective targeted drugs for the future.

Tumours of the Pineal Region

Although tumours of the pineal region are classically considered to be uncommon in children, representing less than 2% of all intracranial tumours (except in Japan and Korea, where they account for 5–10%), their actual frequency may be higher if they are correctly diagnosed. These tumours are a heterogeneous group with both benign and malignant types (Table 14.7) and raise difficult therapeutic problems. Except for astrocytomas, pinealocytomas and perhaps a few

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Markers*</th>
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<tbody>
<tr>
<td>Germ-cell tumours</td>
<td>β-HCG (rare)</td>
</tr>
<tr>
<td>Germinoma</td>
<td></td>
</tr>
<tr>
<td>Typical two-cell type</td>
<td>β-HCG (rare)</td>
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<tr>
<td>Mixed forms</td>
<td></td>
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<tr>
<td>Non-germinomatous</td>
<td>AFP</td>
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<tr>
<td>(non-seminomatous)</td>
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<tr>
<td>Embryonal carcinoma</td>
<td>β-HCG</td>
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<tr>
<td>Teratomas</td>
<td>AFP</td>
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<tr>
<td>Mature</td>
<td>AFP</td>
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<tr>
<td>Immature</td>
<td>AFP</td>
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<tr>
<td>Choriocarcinoma</td>
<td>β-HCG</td>
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<tr>
<td>Yolk sac tumour</td>
<td>AFP</td>
</tr>
<tr>
<td>Mixed malignant</td>
<td>AFP or β-HCG (depending on malignant cell present)</td>
</tr>
<tr>
<td>GCT</td>
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</table>

*Markers are present only in some cases. β-HCG = human β-chorionic gonadotrophic hormone; AFP = α-fetoprotein hormone. In rare cases only.
differentiated teratomas, they are malignant tumours. The clinical features of pineal tumours are described in the account of germ cell tumours below.

**GERMINAL CELL TUMOURS**

**INCIDENCE**

Germ cell tumours are by far the most common pineal region tumours. Intracranial germ cell tumours represent a rare and histologically heterogeneous group of predominantly midline neoplasms. Incidence varies substantially across the continents, with an overall incidence of 0.6, 1.0 and 2.7 per million per year in North America, Europe and Japan respectively.

**PATHOBIOLoGY OF GERMINAL CELL TUMOURS**

Histologically, these tumours are often segregated into three groups: pure germinoma, teratoma, and non-germinomatous germ cell tumours (NGGCTs). Germinomas are the most common tumour of the pineal region, accounting for one-third to one-half of cases. The typical two-cell type germinoma consists of a mixture of large clear cells and small lymphocyte-like cells. Non-germinomatous germ cell tumours are often mixed tumours and can be composed of any combination of yolk sac tumour, embryonal carcinoma and choriocarcinoma. Confusingly, non-germinomatous germ cell tumours can also contain germinoma or teratoma, or both (Murray et al. 2015).

**CLINICAL FEATURES AND IMAGING OF GERMINAL CELL TUMOURS**

Clinical features are largely determined by their localisation but their histological nature also has a bearing on their symptomatology. The predominant symptoms are related to the effects of increased ICP and hydrocephalus in 90% of patients, including headache, vomiting and lethargy. Partial or complete Parinaud syndrome is present in 50% of cases (Cho et al. 1998). Polyuria and polydypsia are relatively common. Isosexual precocious puberty is a classic finding. Neurological signs at presentation may include ataxia and, sometimes, focal neurological dysfunction.

Imaging features are those of a mass lesion in the pineal region. However, in a significant proportion of germinomas, the tumour is located in the suprasellar region, invading the floor of the anterior third ventricle, even in the apparent absence of a pineal germinoma, the so-called ectopic germinoma. Suprasellar tumours were found in five of 11 cases treated by Janmohamed et al. (2002). These ectopic tumours may be the result of seeding from an undetectable pineal primary.

The neuroimaging features of germinoma are fairly distinctive (Fig. 14.15). They are isointense or slightly hyperintense to brain parenchyma on T1 and T2 sequences (Liang et al. 2002). The tumour presents as a round mass of slightly higher density than the brain, sometimes with small, spotty calcification. This should be distinguished from physiological pineal calcification, which is never present before age 4, and is found in 3% of 5–8-year-olds, 12% of 9–12-year-olds, and 19% of 13–16-year-olds. After contrast, the density increases homogeneously. MRI showing well-defined lesions with homogeneous enhancement. Thirty per cent of pure germinomas are bifocal with an additional suprasellar component. The tumour is highly invasive, and tumour cells are almost always present in the CSF although distant metastases to the spine are rare (2–15%); seeding is mainly along the third and lateral ventricles producing a hyperintense rim around the ventricular cavities on enhanced images. Extraneural metastases are rare.

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**Figure 14.15 Pineal germinoma.** (a) T2-weighted sagittal image after gadolinium enhancement showing a tumour of heterogeneously high signal compressing and pushing down and forward the quadrigeminal plate causing hydrocephalus. (b) Frontal view showing the mass and hydrocephalus from aqueductal stenosis.
On neuroimaging, NGGCTs present as heterogeneous masses with areas of high signal due to calcification, haemorrhage, high-protein fluid or fat. A cystic component is present in many cases. Most of them are malignant and the prognosis without therapy is dismal.

TREATMENT OF GERMINAL CELL TUMOURS

The first steps in management are to treat obstructive hydrocephalus (if present) in the acute setting and to obtain a diagnosis. Concepts regarding treatment of these tumours have changed considerably over the past two decades. Tumour markers (alpha-fetoprotein or β-HCG) may be found in CSF and/or serum (Calaminus et al. 2005). Patients with serum or CSF tumour marker concentrations below national protocol thresholds require surgical biopsy for intracranial germ cell tumour diagnosis, regardless of imaging findings. Conversely, patients with consistent radiological imaging and elevation of serum or CSF tumour markers above nationally defined protocol thresholds do not require surgical biopsy for intracranial germ cell tumour diagnosis. Instead, treatment may be initiated, based on the diagnosis suggested by the markers (Murray et al. 2015). Surgical approaches with irradiation in combination with chemotherapy have become the accepted treatment for some types, whereas irradiation alone or chemotherapy alone tended to be reserved for localised germinomas. Current surgical techniques also include neuro-endoscopic biopsy (Gangemi et al. 2001; Pople et al. 2001) or resection and stereotactic surgery (Hasegawa et al. 2003).

Germinomas are exceptionally sensitive to both radiotherapy and to platinum-based chemotherapy but the GCT-96 trial showed that ventricular recurrences sometimes occurred after local radiotherapy. The regimen used in the subsequent GCT II trial has achieved excellent cure rates with a regimen of whole ventricular irradiation with 24Gy plus a 16Gy boost to the involved field. Comparison of whole-ventricular-plus-involved-field radiation with chemotherapy plus lower dose irradiation to the involved field alone has not yet revealed any difference between these treatment options in respect of long-term neurocognitive function. Irradiation alone is reported to give remission rates of the order of 90%. A 2015 report of a Delphi consensus (Murray et al. 2015) has made a number of statements regarding the contemporary standard of care for germ cell tumours. It states that patients with intracranial germinoma should receive radiotherapy to maximise their chance of cure. Focal radiotherapy fields alone are insufficient localised germinoma, and whole ventricular radiotherapy is required while chemotherapy is accepted as an effective strategy to reduce the dose of radiotherapy. Patients with intracranial germ cell tumours containing malignant non-germinomatous components should have residual disease surgically resected before completion of therapy and receive a combination of chemotherapy and radiotherapy. If they also have metastatic spread, their treatment should include craniospinal radiotherapy. After completion of therapy, tumour markers may be predictive of recurrence before the presence of clinical or radiographic evidence. For NGGCTs, high-dose chemotherapy with haematopoietic stem cell rescue should be employed at relapse with surgery and additional radiotherapy where feasible (Murray et al. 2015).

OUTLOOK OF GERMINAL CELL TUMOURS

Depending on the histological nature, the 5-year actuarial survival rates in the study of Ogawa et al. (2003) were 100% for benign tumours, 68% for those of intermediate severity and 8% for those graded as of poor prognosis. More recent studies, employing treatments as per the consensus views cited above, report 5-year event-free survival rates in excess of 70% for ‘standard-risk’ NGGCT ands good rates of salvage when more intensive therapy is given at the time of relapse (Murray et al. 2015).

OTHER PINEAL TUMOURS

Parenchymatous Tumours of the Pineal Body

Account for only a minority of pineal region tumours. Pinealoblastomas are benign tumours. Pinealoblastomas are malignant and tend to metastasise along the CSF pathways especially to the walls of the ventricles (Cuccia et al. 2006).

Astrocytomas of the Pineal Region

Are mostly benign tumours that run a slow course and may present as detectable masses or more rarely as small ‘pencil gliomas’ of the aqueduct with a picture of apparently pure aseptic meningitis. Biopsy is not required when there is a classic radiological appearance and hydrocephalus is best managed with an endoscopic IIIrd ventriculostomy. Radiological surveillance is generally the accepted management. An occasional anaplastic astrocytoma may have a malignant course. In most cases, astrocytomas present as isodense tumours of small to moderate size with some enhancement after contrast administration. Very small astrocytomas are best demonstrated by T2-weighted sequences on MRI, which is particularly useful to detect small intrinsic tumours of the cerebral peduncles or quadrigeminal plate. Surgical resection is indicated for extrinsic astrocytomas that are growing.

Cysts of the pineal region, although they are not really tumours, may present in the same manner. Many of them are fortuitously found on neuroradiological examination and are asymptomatic. Mandera et al. (2003) studied 24 cases, including 17 in female patients. Six required surgical treatment. Monitoring of these lesions is advised as they may be associated with pinealocytoma. No treatment is required but longitudinal follow up is advised. Large symptomatic cysts should be surgically managed. Single or multiple cysts in the pineal region are common in Alacridi syndrome. Ectopic retinoblastoma may involve the pineal body. In association with bilateral ocular retinoblastoma, it is known as ‘trilateral retinoblastoma’. 
OTHER TUMOURS OF THE IIIrd VENTRICLE AND SELlar REGION

Adenomas

Pituitary adenomas are rare in infancy and childhood, and the majority of cases are seen in older children and adolescents (Pandey et al. 2005). The clinical features of adenoma include endocrine disturbances and visual defects. The various types encountered in adults can also occur in the paediatric age range.

Most pituitary tumours are non-functioning adenomas. Prolactin secreting adenomas (prolactinomas) are the most frequent functioning adenoma. They usually present in adolescents as delayed growth and puberty, and amenorrhoea (Duntas 2001; Cannavo et al. 2003). Endocrine investigations reveal a very high level of prolactin often with low levels of growth hormone, TSH and ACTH. Cushing disease is a common cause of Cushing syndrome and occurs as a result of ACTH-producing adenoma in the anterior pituitary gland. Growth hormone-producing adenomas are also quite rare in childhood. They may be associated with acromegaly (in adults) or gigantism (in children).

Clinical features and imaging of adenomas

Most patients present with endocrine disturbance or visual field defects such as bitemporal hemianopia from impingement on the optic chiasm. MRI is the imaging investigation of choice for suspected pituitary disease. Occasionally CT may be valuable in identification of the bony anatomy. Adenomas are typically hypodense on T1-weighted sequences, while their appearance is more variable on T2-weighted images. A convex upper margin of the gland and an increased vertical diameter and surface of the pituitary image for age are characteristic.

Treatment of adenomas

Therapy is mainly surgical. The most common surgical approaches are endo-nasal trans-sphenoidal, using either an endoscopic approach or a microsurgical approach to the sella. Occasionally, craniotomy is required for giant tumours. Irradiation is occasionally required although repeat surgical resection is the preferred option. Cabergoline, a dopamine antagonist inhibitor of the synthesis and release of prolactin, may dramatically reduce the size of large prolactinomas and is the treatment of choice for prolactinomas.

An excellent review of the surgical management of pituitary tumours in adults can be found in Schmidek and Sweet’s book (Vaughan et al. 2012). These techniques apply, broadly speaking, to paediatric patients.

Hypothalamic Hamartomas

Pathobiology

Hypothalamic hamartomas are ectopic masses of neuronal and glial tissue that may be small and pedunculated or sessile and relatively large. They arise from the region of the tuber cinereum or mammillary bodies and develop into the interpeduncular cistern. Their histological structure resembles that of grey matter with varying proportions of neurons, glia and fibre bundles. They do not behave as true tumours. Rather, they grow at approximately the same rate as the rest of the encephalon and never produce symptoms or signs of nerve tissue compression. Rare cases are part of the Pallister–Hall syndrome that also includes polydactyly and imperfect anus. Sixteen cases were studied by Boudreau et al. (2005), who found these cases to be of lesser severity on average than isolated cases.

Clinical features and imaging of hypothalamic hamartomas

Clinically, hypothalamic hamartomas may remain asymptomatic. In infants and young children they are often associated with a peculiar epilepsy syndrome. Precocious puberty is the most common clinical manifestation. Its central origin is demonstrated by the increased levels of gonadotropins. The epileptic syndrome associated with hamartomas has an early onset, usually before 2 years of age, and is characterised by the frequently repeated occurrence of attacks of laughter (gelastic fits) (Chapter 16). Epilepsy in hamartomas is rarely controlled completely with drugs (Arzimanoglou et al. 2003; Freeman et al. 2004). The imaging appearance of hamartomas is characteristic, with a well-limited rounded isodense mass surrounded by CSF in the interpeduncular cistern. On MRI the mass is clearly definable in multiplanar sequences. A more intense signal than the surrounding brain is present on T2-weighted sequences in 93% of cases, and a low signal on T1 sequences in 74%. Spectroscopy may show a decrease in N-acetyl aspartate and in myoinositol (Arzimanoglou et al. 2003; Freeman et al. 2004). Small hamartomas may be lateralised, difficult to visualise and require especially careful MRI studies.

Treatment of hypothalamic hamartomas

Resection of the hamartoma is difficult but can control the epilepsy (Polkey 2003), although it does not always result in disappearance of the seizures. Endoscopic approaches to the IIIrd ventricle are often employed. Disconnection of the hamartoma is also effective. Fohlen et al. (2003) reported on 18 cases so treated; nine became seizure-free and marked improvement was obtained in the remaining patients. However, seizures may originate in the hamartomatous tissue, and resection of the tumours may be effective. Gamma knife treatment has also been used (Regis et al. 2004). Callosotomy has been suggested for resistant seizures but is of limited value. (For a more detailed review of surgical treatment options see Chapter 16 and Arzimanoglou et al. 2016.)

Chordomas

Pathobiology

Intracranial chordomas are extra-axial lesions generally located along the clivus. Chondromas, developing from the
spheno-occipital synchondrosis, are indistinguishable from chordomas, unless associated with Ollier disease. Nine familial cases are on record; in one of which a tumour suppressor locus (1p36) was mapped (Miozzo et al. 2000).

**Clinical features and Imaging of Chordomas**
Chordomas, when located anteriorly, may give rise to symptoms and signs similar to those of other parasellar tumours. More posteriorly located chordomas produce palsies of the lower cranial nerve pairs. Plain skull X-rays may show destruction and deformation of the sella turcica and body of sphenoid bone. On CT, chordomas present as well-delineated masses with frequent calcification and contrast enhancement.

**Treatment of Chordomas**
Surgical resection via an endoscopic approach is often performed although complete resection can be very challenging. Proton beam radiotherapy is often given to control tumour growth.

**Other Parasellar Tumours**
*Colloid cysts of the third ventricle* are very rare in children (see Intraventricular Tumours section).
*Choroid plexus papillomas of the third ventricle* have been reported (see Intraventricular Tumours section).
*Paranasal sinus mucoceles* are rare pseudo-tumoural lesions in children, presenting as dilated fluid-filled masses due to the accumulation of mucus and secretions within an occluded sinus cavity (Perez Gonzalez et al. 2002). All sinuses including the sphenoid sinus may be involved. Mucoceles result from infection (Uren and Berkowitz 2003), trauma, congenital deformity of the ostium, or cystic degeneration of the mucosa. Mucoceles may present with ocular motor palsies, decrease in visual acuity and various eye signs. On CT they present as spontaneously dense areas with possible intracranial extensions.

---

**Tumours of the Cerebral Hemispheres**

**Incidence**
Tumours of the cerebral hemispheres are more common in younger than in older children. Their clinical manifestations are polymorphic with a high incidence of focal neurological symptoms and signs. Most supratentorial tumours are gliomas. Low grade astrocytomas (WHO grades I and II) are the most frequent hemispheric tumours, accounting for 21% of all supratentorial neoplasms in children.

**Gliomas of the Cerebral Hemispheres**

**Pathobiology**
In contrast to the 2007 WHO classification of tumours, WHO CNS 2016 groups all diffusely infiltrating gliomas, whether astrocytomas or oligodendrogliomas, together based not only on their growth patterns and behaviours but also on their shared mutations in the IDH1 and IDH2 genes. Diffuse gliomas therefore now include WHO Grade II and III, Grade IV tumours and the related diffuse gliomas of childhood. Fibrillary astrocytomas, a term dropped from WHO CNS 2016, fall within this group (Louis et al. 2016). The great majority of Grade II and III diffuse astrocytomas are IDH-mutant while the majority of IDH-wildtype diffuse gliomas are glioblastomas. The term ‘gliomatosis cerebri’ has been dropped although the growth pattern to which it referred is mentioned as a special pattern of spread in some diffuse gliomas that is defined by involvement of at least three cerebral lobes with frequent bilateral growth and regular extension to involve infratentorial structures (Louis et al. 2016).

One narrowly defined group of tumours, primarily occurring in children, is characterised by K27M mutations in the histone H3 gene H3F3A or closely related HIST1H3B gene and is termed *diffuse midline glioma, H3K27M mutant*. Besides their diffuse growth pattern, they typically develop in the midline (thalamus, brainstem or spinal cord). This group includes tumours previously referred to as ‘diffuse, intrinsic, pontine glioma’, another appellation rendered obsolete by the 2016 classification (Louis et al. 2016).

Not included in the above are pilocytic astrocytomas, pleomorphic xantho-astrocytomas and subependymal giant cell astrocytomas all of which have a more circumscribed growth pattern, lack IDH family gene family mutations and frequently have BRAF gene alterations or TSC1/TSC2 mutations. Diffuse astrocytomas and oligodendrogliomas are now therefore classified as being more alike than are diffuse and pilocytic astrocytomas. Pilomyxoid astrocytomas have extensive histological and genetic overlap with pilocytic astrocytomas and may be better classified as Grade I rather than Grade II but are currently ungraded (Louis et al. 2016).

**Low-Grade Gliomas**

**Incidence**
Cortical tumours tend to present later in childhood and early adolescence with focal neurological signs or epilepsy. Their resectability is determined by the eloquence of their anatomical location. Histological grading in cortical location is very
important as their presentation during adolescence raises the possibility of non-pilocytic tumours with the associated risk of subsequent malignant transformation.

**Pathobiology**

The predominant types are pilocytic or diffuse gliomas as discussed in sections on cerebellar and brainstem tumours above. Rare subtypes include SEGA associated with tuberous sclerosis complex, pleomorphic xanthoastrocytoma, cerebral astrocytoma with extensive calcification, mixed neuronal-glial tumours including ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET) and desmoplastic infantile astrocytoma/ganglioglioma (DIA/DIG).

**Clinical Features and Imaging**

The clinical presentation of parenchymal supratentorial tumours can be due to generalised raised ICP, focal neurological deficit or seizures. The presentation of the focal neurological deficit depends more on the location of the tumour than on its histological nature. Signs of high ICP and focal neurological manifestations may occur in isolation or in various combinations. Headaches, nausea and vomiting may be the presenting manifestations in about 20% of patients, mainly those with malignant tumours.

Epileptic seizures are the most common neurological manifestation, particularly in slowly growing, benign tumours such as low grade astrocytomas and oligodendrogliomas. Seizures are mostly focal. Partial motor and partial complex seizures are the most frequently observed types. Sensory seizures may be especially suspect. On the other hand, uncinate seizures may not be more likely than other types to be due to brain tumours. The occurrence of generalised seizures and of bilateral paroxysmal EEG abnormalities does not exclude the possibility of a tumour (Bourgeois et al. 1999). Long-standing epilepsy used to be frequent in patients with brain tumours but the advent of CT and MRI has led to earlier recognition of the underlying tumour. Epilepsy is the first presenting symptom in around 9% of childhood brain tumours and will occur at some point prior to diagnosis in about 15% of cases. In contrast to other symptoms of a brain tumour, it often occurs without other suggestive symptoms or signs, and the importance of imaging for early diagnosis, especially in those with onset in infancy or with any focal clinical or EEG features, cannot be overemphasised (Wilne et al. 2006).

Localised deficits are less frequently the presenting manifestation of supratentorial diffuse gliomas and are apt to be rather late features. However, hemiparesis, hemianopia and language disturbances may occasionally be the first clinical manifestation, especially with malignant neoplasms.

Although modern neuroimaging techniques have considerably facilitated the diagnosis of supratentorial tumours, the interpretation of images remains difficult as numerous lesions of different origins can give rise to similar radiological pictures. The CT appearance of benign astrocytomas is variable. In a majority of cases, the lesions are well defined and regular in shape. They appear hypodense without contrast enhancement (Fig. 14.16), and their density may increase in a nonhomogeneous manner after contrast injection (Fig. 14.17). Many are cystic with only a small enhancing nodule. False negatives and false positives may occur. Approximately 15% of gliomas are not detected on CT. MRI is more sensitive than CT and gadolinium-enhanced MRI is very effective in the detection of...
Figure 14.17 Large pilocytic astrocytoma of the left temporal lobe. T2-weighted showing that the tumour is heterogeneous with a solid central part and cystic formation. The posterior cyst is thin-walled; the anterior cavity has a thick wall with irregular contrast enhancement and pushes the median vessels toward the right. In spite of its huge volume, the histological nature of the tumour was not malignant.

gliomas although scans may be difficult to interpret. In some cases, oedema can give an intense signal identical to that of the mass itself on T2-weighted sequences.

TREATMENT

Surgery is clearly the initial approach, can give excellent results especially in astrocytomas and oligodendrogliomas and can be the definitive treatment for astrocytomas (Fig. 14.16). Progression-free survival at 5 years of over 90% after surgery without, in most cases, radiotherapy has been reported in several series (e.g. Shaw and Wisoff 2003). However, complete excision may not be possible. Adjuvant treatment after partial excision is commonly with radiation, which has some effect on tumour volume, but chemotherapy currently has a major role as an adjuvant treatment as it is effective in children and avoids radiation damage (Fouladi et al. 2003b) and combined treatment with surgery followed by chemotherapy is often employed. Cisplatin and etoposide seem especially effective (Massimino et al. 2002).

The rare subtypes of low grade gliomas listed above are generally treated surgically where possible and the role of chemotherapy has not been extensively studied. SEGAs associated with TSC types 1 and 2 have been identified as being sensitive to mTOR inhibitors. Everolimus has been shown to shrink unresectable SEGAs and contribute to enhanced epilepsy control in patients with tuberous sclerosis in the EXIST trials. There was no association between TSC mutation subtypes and clinical responses (Kwiatkowski et al. 2015).

OUTLOOK

The prognosis of astrocytomas is clearly better in children than in adults. In a series of 71 children with supratentorial low grade astrocytomas, Pollack et al. (1995) found overall survival rates at 5, 10 and 20 years respectively of 95%, 93% and 85%, and progression-free rates of 88%, 79% and 76%. The major predictive factor was the extent of surgical resection. Radiation therapy was not related to outcome. Pilocytic astrocytomas had better prognosis than non-pilocytic gliomas. A generally similar conclusion can be drawn from five prospective trials (four in adults and one in children) that found no significant difference in survival between patients who did or did not receive radiation after surgery, although radiation seemed to reduce tumour volume in adults (Fernandez et al. 2003; Shaw and Wisoff 2003).

Pleomorphic xantho-astrocytomas have attracted some attention despite their rarity. They occur in young children, are almost always supratentorial, are frequently located in the temporal or frontal lobes, and present commonly as isolated seizures. They share many clinical features with the epileptogenic tumours such as ganglioglioma and developmental neuroepithelial tumours (see below) despite their specific histological features (Fouladi et al. 2001; Im et al. 2004).

OLIGODENDROGLIOMAS

PATHOBIOLOGY

These are slow-growing tumours with a strong tendency to calcify and are relatively rare in childhood (about 20% of all supratentorial tumours). As discussed in the Gliomas of the Cerebral Hemispheres section, they are classified as part of the ‘diffuse glioma’ family. They are subclassified as either IDH-mutant and 1p/19q co-deleted or as not otherwise specified. Reports of associations between histological variants of oligodendrogliomas, partial deletions of chromosomes 1p or 19q, and prognosis in adults are discussed in Aldape et al. (2007). However, these deletions seem to be rare in children (Kreiger et al. 2005).

CLINICAL FEATURES AND IMAGING

The majority of tumours are located in the frontal lobe and 50–70% of cases present with convulsive seizures. The CT or MRI appearances of oligodendroglioma are usually characteristic, with hypointensity on T1 sequences and high signal on T2 images. About 40% are calcified and 60% have well-defined margins (Fig. 14.18). Less than half produce a mass effect and less than a quarter of cases enhance with contrast. They may produce thinning of the inner skull table, indicating a slowly enlarging lesion as may also be seen with benign astrocytomas and with dysembryoplastic neuroepithelial tumours. These are described in Chapter 16 as they usually present with isolated epilepsy.
Part VI  Tumours and Vascular Disorders

Tumours and Vascular Disorders

Pathobiology

Glioblastoma, IDH-wildtype (about 90% of cases) predomi-
nates in patients aged more than 55 years whereas epithelioid
glioblastoma, which is a newly recognised variant of glioblas-
toma, IDH-wildtype, newly recognised in WHO CNS 2016,
is more common in children and younger adults. It typically
presents as superficial cerebral or diencephalic masses and is
often accompanied by a \textit{BRAF} mutation (Louis et al. 2016).

Some of these arise from lower grade pleomorphic xantho-
astrocytomas (Louis et al. 2016). Glioblastoma, IDH-
mutant also arises preferentially in younger patients correspon-
ding closely to the phenomenon of glioblastoma occurring in
the context of a prior lower grade, diffuse glioma (Louis et al.
2016).

Clinical features and imaging

Seizures are the presenting feature in about one-third of
patients, but headache, hemiparesis and personality changes
are more frequent. Contrast enhancement is common in glio-
blastoma (Fig. 14.19) but may be absent in anaplastic astro-
astrocytomas. Diffusion-weighted MRI and magnetic resonance

Treatment and outlook

The outcome following surgery is usually good, especially in
young patients and the tumours tend to remain stable for long
periods even following only partial resection, although a poor
outcome is associated with coexisting neurological deficit at the
time of diagnosis and the presence of nuclear pleomorphism
of the tumour on histological examination. This favourable
outcome was confirmed by Peters et al. (2004) who reported
post-surgery survival in 22 of 26 children with peripheral
tumours. This was in marked contrast with the low survival
rates for central oligodendrogliomas involving the basal nuclei.
The prognosis of malignant oligodendrogliomas is poor.

HIGH-GRADE GLIOMAS

Incidence

High-grade astrocytomas such as anaplastic astrocytomas
(WHO Grade 3) and other malignant gliomas such as glio-
blastoma multiforme (WHO Grade 4) are uncommon in chil-
dren, accounting for only 7–11% of primary brain neoplasms
in this age range.

Figure 14.18 Oligodendroglioma of the left cerebral hemisphere.
T2-weighted image showing heterogeneous areas of high signal
and faintly visible areas of low signal. CT showed areas of high
density indicating the presence of calcification at the periphery of
the tumour.

Figure 14.19 Extensive glioblastoma multiforme in 9-year-old girl
who had been treated for acute lymphocytic leukaemia at age
3 years and was subsequently intellectually impaired with a leu-
koencephalopathy due to methotrexate and X-irradiation. This is
typical of a ‘second tumour’ probably induced by initial therapy.

Figure 14.18 Oligodendroglioma of the left cerebral hemisphere.
T2-weighted image showing heterogeneous areas of high signal
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3 years and was subsequently intellectually impaired with a leu-
koencephalopathy due to methotrexate and X-irradiation. This is
typical of a ‘second tumour’ probably induced by initial therapy.
spectroscopy can help establish the nature of the tumour (Chang et al. 2003). However, large enhancing tumours are not necessarily malignant (Fig. 14.17).

**TREATMENT**

Surgical treatment is usually followed by radiation therapy. There is currently an increasing tendency to use chemotherapy, which has been found to be effective in improving the overall survival of children with these tumours (Massimino et al. 2005), in contrast to what has been reported in adults. It is also increasingly used to delay or avoid radiotherapy for high-grade tumours.

**OUTLOOK**

Although the prognosis is often more favourable than in adults with histologically similar tumours, it remains poor and even with high-dose chemotherapy, the results are variable and mortality remains significant. The actuarial probability of survival is 32% at 3 years after surgery. An adverse outcome has been found to be significantly correlated with overexpression of the P53 protein in the tumours independently of histology, age and tumour location (Pollack et al. 2002).

**SUPRATENTORIAL EPENDYMOMA**

As stated in the section of Ependymomas of the Posterior Fossa, the majority of supratentorial ependymomas in children belong to the genetically defined 2016 WHO CNS classification subtype ependymoma, RELA fusion positive (Table 14.5)(Louis et al. 2016). In contrast to posterior fossa ependymomas, the peak age at onset is in adolescence. Metastases from supratentorial ependymomas are mainly intracranial, in contrast with posterior fossa ependymomas in which metastases are predominantly spinal. As discussed in posterior fossa ependymomas, gross total surgical resection appears most clearly to be associated with higher survival rates and to be technically achievable in that minority of ependymomas that are supratentorial in location (Cage et al. 2013).

**OTHER TUMOURS OF THE CEREBRAL HEMISPHERES**

**DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOUR**

**INCIDENCE**

Dysembryoplastic neuroepithelial tumour (DNET), like gangliocytomas and gangliogliomas, are classified as neuronal and mixed neuronal-glial tumours. Indeed, different investigators may employ any of these terms to describe a particular tumour even though they are different tumour types. Because most of these lesions are highly epileptogenic they are also discussed in Chapter 16.

**PATHOBIOLOGY**

They include a mixture of neuronal and glial elements, both oligocytes and astrocytes, and appear to be of developmental origin. They may be associated with some oedema of the white matter. However, a few mitoses can be seen. It is likely that a significant proportion of the cases formerly diagnosed as low grade oligoastrocytomas were in fact DNETs. These tumours are located cortically but may encroach on the underlying white matter. The use of the term oligoastrocytoma is ‘strongly discouraged’ in WHO CNS 2016 classification (Louis et al. 2016).

**CLINICAL FEATURES AND IMAGING**

These tumours manifest clinically as isolated epilepsy (see Chapter 16). They are often found in the temporal or frontal lobes of children and adolescents with chronic focal seizures of early onset (Giulioni et al. 2005). They are of mixed density on CT, and only 18% enhance after contrast infusion. A quarter of them are calcified, and one-third produce a focal cranial deformity as a result of erosion of the inner skull table. They give a mixed signal on MRI, usually with low signal on T1-weighted sequences and sometimes high signal on T2-weighted sequences (Fig. 14.20).

**TREATMENT AND OUTLOOK**

These lesions have little or no tendency to grow and usually remain stable on repeat examinations. Some of these tumours develop in areas of cortical dysplasia. Surgical removal, even if subtotal, may give good results without recurrences and good seizure control. Irradiation is clearly contra-indicated. When manifesting with seizures, DNETs need to be promptly evaluated by a paediatric epilepsy surgery team (see Chapter 16).
temporal lobe origin. They occur mainly in young children or even in neonates without any sign of increased pressure. The diagnosis is often difficult. CT typically reveals hyperdense cortical lesions with gyriform or serpiginous outlines without marked mass effect. Most lesions are difficult to identify on T1-weighted MRI sequences and may have low, intermediate or increased signal on T2-weighted images. The rare desmoplastic infantile ganglioglioma (Khaddage et al. 2004) is seen almost exclusively below 2 years of age. It presents as a large tumour with a large cystic component and a solid component that takes up contrast on T1 sequences and appears hyperintense on T2 sequences, often with meningeal enhancement (Tamburrini et al. 2003; Trehan et al. 2004). Its main interest is that its diagnosis is difficult and it is often mistaken for a malignant tumour. Yet, resection leads to cure.

TREATMENT AND OUTLOOK
Surgical removal often results in the cure of epilepsy (see also Chapter 16). Removal of the lesion was associated with relief of seizures in 84% of 184 patients with a median follow-up at 8 years post-surgery (Luyken et al. 2004). The long-term prognosis is favourable: the survival rate at 7.5 years was 97% in that series, even in cases in which the tumour was not totally removed.

MENINGIOMAS
INCIDENCE
Meningiomas are relatively rare in children at which age the incidence is 0.1 per 100,000 (Sugden et al. 2014), representing less than 2% of intracranial tumours. Their incidence is increased by radiation exposure, increasing with time since and dose of radiation. The issue of screening survivors of childhood brain tumours for meningiomaticous second tumours has been aired (Sugden et al. 2014). It is also a frequent tumour in patients with NF2 (Sadetzki et al. 2002; Ruggieri et al. 2005) (Chapter 4).

PATHOBIOLGY
Most meningiomas are found in the convexity of the brain, but meningiomas found in childhood are characterised by a higher incidence, compared to adults, of location within the lateral ventricles or the posterior fossa, absence of a dural attachment, and cyst formation. Perry and Dehner (2003) reported 13 cases and reviewed the literature extensively. Im et al. (2001) emphasised the large size of many of these tumours, their unusual location, the frequency of calcification and of cyst formation in the gingiva and characteristic radiological appearance. Most meningiomas in childhood are of the fibrous type, consisting of spindles of prominent fibroglia. The angiomatous type is much less common.

CLINICAL FEATURES AND IMAGING
Increased ICP is responsible for most clinical manifestations but seizures are the presenting feature in 8–31% of cases. Intraventricular meningiomas are apt to present with signs of intermittent obstruction of CSF outflow tracts. Optic canal or orbital tumours produce central scotomas or variable field defects. They may be difficult to distinguish from optic pathway tumours. Hyperostosis or bone destruction favour the diagnosis of meningioma. CT clearly demonstrates most meningiomas especially after contrast enhancement. The CT picture, however, may be less characteristic in children than in adults. Large cystic formations are frequent, especially in children under 2 years of age. MRI showing a decreased T1 and increased T2 signal, and usually demonstrates heterogeneity of the tumour due to tumour vascularity, cystic degeneration and calcification. It enables better delineation of the limits of the lesion and helps to indicate whether the tumour is intra- or extra-axial.
Chapter 14 Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri

TREATMENT
Therapy is basically surgical but radiation, especially stereotactic irradiation, may play a role for patients in whom histology suggests a more aggressive course and in recurrent tumours that cannot be resected. The features and management of meningiomas as one type of post-irradiation secondary tumours have been reviewed (Sugden et al. 2014).

PRIMARY CEREBRAL NEUROBLASTOMAS

INCIDENCE AND PATHOBIOLOGY
Primary cerebral neuroblastomas are rare. They occur in the first decade of life in 81% of cases and in 20% before the age of 2 years. Most are primary (Etus et al. 2002; Yaris et al. 2004). A few are cerebral relapses or metastases of peripheral neuroblastoma (Porto et al. 2005a).

CLINICAL FEATURES, TREATMENT AND OUTLOOK
The clinical picture is that of cerebral hemispheric tumours in general. Survival following surgery and irradiation with or without chemotherapy reaches 3 years in 60% of patients and exceeds 5 years in 30%.

TUMOURS OF THE BASAL GANGLIA AND THALAMUS

INCIDENCE
These tumours represent 2–6% of intracranial tumours in children. Most are astrocytomas of various grades, from benign pilocytic lesions to anaplastic astrocytomas and glioblastoma multiforme.

CLINICAL FEATURES AND IMAGING
The most common manifestation is progressive hemiparesis, which may be associated with unilateral dystonia or intention tremor. The majority have signs of corticospinal tract involvement and about 10% present with a movement disorder, most commonly tremor or dystonia. Homonymous hemianopia, nystagmus and hearing loss may be observed. Sensory manifestations are exceptional. Martinez-Lage et al. (2002) studied 20 patients, four of whom presented with acute manifestations: intracranial hypertension was present in 13, motor deficit in eight, seizures in seven, behavioural or cognitive disturbance in five, and abnormal movements in only two patients.

The diagnosis is readily suggested by CT or MRI, when the tumour is hypodense and when contrast enhancement is present (Lefon et al. 2000) (Fig. 14.21). The latter may occur in a ring-like manner. In some cases the tumour is infiltrating and its density does not differ, even after contrast injection, from that of the surrounding brain. In such cases recognition of the mass effect caused by the tumour is the only diagnostic criterion. Bilateral thalamic gliomas may raise a difficult diagnostic problem and usually confer a poor prognosis (Gudowius et al. 2002).

TREATMENT
Complete surgical removal of tumours of the basal ganglia is challenging and may lead to significant morbidity. Stereotactic biopsy is often used as an alternative to attempted resection and blind radiotherapy is best avoided. Irradiation is reserved for malignant tumours.

INTRAVENTRICULAR TUMOURS

Tumours of different histological types can be located within the lateral ventricles. These include choroid plexus papillomas (CPP) and carcinomas, intraventricular meningiomas, central neurocytomas, ependymomas and intraventricular cysts.

CHOROID PLEXUS PAPILLOMAS

INCIDENCE
Choroid plexus papillomas (CPPs) arise from the epithelium of the plexus and are relatively common in infants, about 20%
occurring below 1 year of age, but rare in older children. They are large, cauliflower-like tumours that present the structure of normal choroid plexus with a considerable degree of hyperplasia. Papilloma of the choroid plexus of the fourth ventricle is rare in children, in whom most papillomas arise from the lateral ventricle (Rostasy et al. 2003).

**Clinical features and Imaging**

The usual manifestation of CPP in infants is hydrocephalus (Chapter 7), which is generally rapidly evolving and may be accompanied by papilloedema, an uncommon finding in hydrocephalus arising without an intraparenchymal mass. The diagnosis is easy because papillomas present as large intraventricular masses with massive enhancement after contrast injection (Fig. 14.22). The hydrocephalus usually results from hypersecretion of CSF by the tumour but it may also be due to meningeal fibrosis resulting from haemorrhage from the tumour. In older children, choroid plexus tumours are more likely to be located in the fourth ventricle or the temporal lobe and produce seizures rather than hydrocephalus. Calcification is sometimes present.

**Treatment**

Excision of the papilloma is the treatment of choice. They are extremely vascular tumours with substantial peri-operative mortality usually resulting from haemorrhage. The risk of this may be increased by proceeding immediately to definitive surgery without first putting interim treatment of hydrocephalus in place. Pre-operative embolisation of the posterior choroidal vessels may reduce the risk of blood loss intraoperatively. Radiation therapy is reserved for tumours having malignant histological patterns.

**Outlook**

Postoperative complications are unfortunately not rare (Nagib and O’Fallon 2000; Kumar and Singh 2005). Hydrocephalus is common despite complete removal of the tumour and a shunt may be required.

**CHOROID PLEXUS CARCINOMA**

**Incidence and Pathobiology**

Choroid plexus carcinoma is a rare, malignant tumour accounting for about 40% of choroid plexus tumours. Neuropathological features include high cellularity, anaplasia and necrosis. Metastatic spread is common.

**Treatment and Outlook**

Complete surgical resection is associated with a higher likelihood of long-term survival. The benefit of radiotherapy and chemotherapy is disputed but a 5-year survival rate of 38% following the intensive ‘Headstart’ chemotherapy regimen has been reported (Zaky et al. 2015).

**CENTRAL NEUROCYTOMA**

**Incidence and Pathobiology**

Central neurocytomas (CNCs) are rare tumours thought to arise from the septum pellucidum. They most commonly arise in the lateral ventricles and in adolescence but are also seen in other locations and in other age groups.

**Clinical Features and Imaging**

The clinical presentation is usually with symptoms of raised ICP secondary to hydrocephalus and imaging typically showing heterogeneous masses that are iso-intense or slightly hyperintense on T1-weighted MRI and iso-intense to hyperintense on T2-weighted imaging. Contrast enhancement is variable but usually moderate. The presence of cysts, calcification,
haemorrhage or tumour may result in hypo-intensity. CNCs may be misdiagnosed as oligodendrogliomas or ependymomas on the basis of their CT or MRI characteristics. Proton MRS has recently emerged as a promising tool for diagnosis of CNC and showing high glycine, increased choline and alanine and decreased N-acetylaspartate and creatine/phospho-creatin peaks (Patel et al. 2013).

**TREATMENT AND OUTLOOK**

Surgery is the primary treatment for CNC and gross total resection is associated with a favourable prognosis. In patients where this is unattainable, subtotal resection with adjuvant radiotherapy or radiosurgery has been shown to offer better rates of control and survival than surgery alone. Adjuvant radiation treatments have also been shown to be useful in cases of tumour recurrence and may have a role as primary treatments for smaller tumours (Patel et al. 2013).

**COLLOID CYSTS OF THE IIIrd VENTRICLE**

These tumours occur only very rarely in children. They manifest in children, as in adults, with severe headaches that are often paroxysmal in character and are sometimes precipitated by certain positions or movements of the patient. They may be a rare cause of sudden death in children and adolescents (Kava et al. 2003). Nine familial cases are on record (Partington and Bookalil 2004).

**EMBRYONAL TUMOURS OTHER THAN MEDULLOBLASTOMA**

**EMBRYONAL TUMOURS WITH MULTILAYERED ROSETTES**

**INCIDENCE AND PATHOBIOLOGY**

These are rare, highly malignant (WHO Grade IV) neoplasms that occur mostly in young children but cases exist in older children and young adults. The mean age of a series of cases reported from France was 31 months (Horwitz et al. 2016).

Embryonal tumours other than medulloblastoma have been substantially re-classified in WHO CNS 2016 with removal of the term ‘primitive neuro-ectodermal tumour’, previously recognised as an embryonal tumour distinct from medulloblastoma, from the diagnostic lexicon (although, confusingly, it lives on in ‘SIOP-PNET5-MB’, the name of one of the current treatment trials for medulloblastoma). Many of these tumours display amplification of the C19MC region on chromosome 19 (19q 13.42) and should now be termed embryonal tumours with multilayered rosettes (ETMR). This entity also includes the groups of tumours previously referred to as embryonal tumours with abundant neuropil and true rosettes, and ependymoblastoma. These are now subclassified on molecular genetic features as ETMR, C19MC altered or, in the absence of that genetic feature, as ETMR, NOS (Louis et al. 2016). A further category of embryonal tumours is termed medullopithelioma, a diagnosis based on histological features. Pineoblastomas have been considered alongside embryonal tumours in some series but are classified separately under pineal region tumours.

The typical histological features of ETMRs include small, undifferentiated cells without observable cytoplasm, and dark oval or irregular nuclei with prominent nucleolus (Ellison et al. 2003; Vogel and Fuller 2003). Numerous mitotic figures and necrosis are often present. Occasional focal areas of differentiation toward neuronal or glial lines may often be recognised. By electron microscopy, the tumour cells have been reported to have similarities to the developing cortical plate of the fetus (Ellison et al. 2003; Vogel and Fuller 2003). The defining feature of medullopitheliomas is a distinctive pseudostratified epithelium that is arranging in papillary and tubular structures.

**CLINICAL FEATURES AND IMAGING**

Most ETMRs and medullopitheliomas are located in the cerebral hemispheres but may be found in the posterior fossa (Zagzag et al. 2000). Their clinical features are typically those of malignant supratentorial tumours. Clinical features of raised ICP and focal deficits are more common than seizures. The history is usually very brief. CT may show cystic formation and extensive calcification. Neoplastic meningitis may be the first manifestation.

**TREATMENT AND OUTLOOK**

Treatment is with as complete a resection as possible, followed by irradiation and chemotherapy. Stem cell rescue has permitted the use of increased doses of chemotherapy and/or radiation (Perez-Martinez et al. 2004). With a median follow-up of 70 months, 5-year progression-free survival (PFS) was 40% for all patients and increased to 63% in those patients who received subtotal or total resection and radiotherapy without interruption (Choi et al. 2016). A study of the use of craniospinal radiotherapy with concurrent carboplatin following surgery followed by 6 months of maintenance chemotherapy with cyclophosphamide and vincristine reported 5-year PFS for all patients of 48.7% (62.1% in pineoblastoma and 39.8% in non-pineal tumours). The outcome of this well-tolerated regimen is certainly comparable to those seen with more intensive and longer-duration regimens. Complete surgical resection had a large impact on survival rates (Jakacki et al. 2015). However, for children with a molecularly and histologically well-defined ETMR the prognosis remains poor. The 1-year overall survival (95% Confidence Interval) in the series reported by the French collaborative group was 45% (31–64%) (Horwitz et al. 2016). On multivariate analysis, complete surgical resection, radiotherapy, and high-dose chemotherapy were associated with a better overall survival (Horwitz et al. 2016).
ATYPICAL TERATOID/RHABDOID TUMOURS

Incidence and Pathobiology
Atypical teratoid/rhabdoid tumours (AT/RT) are rare, constituting 5–10% of childhood brain tumours. Like ETMRs, AT/RTs are Grade IV embryonal tumour occurring predominantly in children aged less than 3 years. The diagnosis is now defined by alterations affecting the \( SMARCB1 \) locus on 22q, or, very rarely of \( BRG1 \), leading to loss of \( SMARCB1/INI1 \) protein expression. In the absence of these genetic alterations it is classified as CNS embryonal tumour with rhabdoid features. AT/RTs show similar histology to ETMRs but with the addition of rhabdoid cells with eosinophilic granular cytoplasm and an eccentric nucleus.

Clinical Features and Imaging
The history is usually short and usually includes clinical features of raised ICP. The clinical and radiological features otherwise depend on the tumour location. About half of AT/RTs are found in the posterior fossa, either in the cerebellopontine angle or more midline, and half in the cerebral hemispheres.

Treatment and Outlook
Children aged more than 3 years or whose tumour was totally resected have a relative better prognosis. Incomplete resection and metastatic spread via the CSF are more common in younger patients. Postoperative craniospinal irradiation and high-dose chemotherapy improve survival rates but the quality of survival of infants or pre-school children may be severely compromised by these treatments. Two-year overall survival rates of 70% are reported (Chi et al. 2009) and are significantly better for those aged more than 3 years at diagnosis than for younger patients (89 vs 17%) (Tekautz et al. 2005).

DIFFUSE GLIOMA AFFECTING THE CEREBRUM AND INFRAVENTRIONAL STRUCTURES

Incidence and Pathobiology
The rare neoplastic disorder, involving large parts of the brain in a multicentric or diffuse overgrowth with cells of neuroglial, oligodendroglial or astrocytic lineage (Caroli et al. 2005), is now considered to be the manifestation of a growth pattern found in many types of gliomas, including both IDH-mutant and IDH-wildtype diffuse astrocytic and oligodendrogial gliomas and IDH-wildtype glioblastomas (Louis et al. 2016) (see also the Gliomas of the Cerebral Hemispheres section). The term gliomatosis cerebri has been dropped (Louis et al. 2016).

Clinical Features and Imaging
Corticospinal tract deficits, dementia/intellectual disability, headache, seizures, cranial neuropathy, raised ICP and spinocerebellar deficit each occur in a third or more of patients. The diagnosis is often difficult as imaging is not characteristic, showing areas of nonspecific (diffusely increased) signal. Atypical clinical presentations have been reported, suggesting meningoencephalomyelitis (Jayawant et al. 2001) or even Rasmussen syndrome because of the presence of epilepsy partialis continua (Shahar et al. 2002). The disorder has also been described in a new born infant whose imaging had suggested lissencephaly.

Treatment and Outlook
Chemotherapy has been advised as therapy for children (Sanson et al. 2004) but its benefit is uncertain. Radiotherapy but not chemotherapy is reported to prolong survival in adults with the condition. The prognosis is poor.

DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOUR

Incidence
Diffuse leptomeningeal glioneuronal tumour (DLGNT) is a rare mixed neuronal-glial tumour, newly defined in WHO CNS 2016 (Louis et al. 2016).

Pathobiology
The histological appearance is of monomorphic clear cell glial morphology reminiscent of oligodendroglia. \( BRAF \) fusions and deletions of chromosome 1p and occasionally of 19q, are common but IDH mutations are absent.

Clinical Features, Imaging and Outlook
DLGNT presents as diffuse leptomeningeal disease with or without a recognisable parenchymal component, commonly in the spinal cord and occurring most often in children and adolescents. These tumours typically show relatively slow growth and cause secondary hydrocephalus (Louis et al. 2016).

METASTASES

Intracranial metastases of extracranial tumours are rare in childhood. Wilms tumours, osteosarcoma, rhabdomyosarcoma, melanoma and neuroblastoma are known occasionally to metastasise to the brain. Curless et al. (2002b) found that neuroblastomas, osteosarcomas, melanoblastomas, Ewing sarcomas and germ cell tumours were responsible for most haematogenous metastases in a review of 2040 tumour cases. Intracranial metastases have no distinctive features. They may be single or multiple and present as areas of hypodensity, which enhance following contrast injection, and surrounding oedema.
NON-METASTATIC MANIFESTATIONS OF TUMOURS OF OTHER ORGANS

A proportion of cases of the opsoclonus–myoclonus–ataxia syndrome (see Chapter 12), a syndrome confined to infancy, are associated with paraspinal neuroblastoma. Imaging of the CNS in this condition is always completely unrewarding as the underlying cause is not to be found there. Rates of survival from the tumour in this clinical setting are very high. The syndrome, although sensitive to immunosuppressive treatment with glucocorticoids, usually has long-term neurocognitive sequelae.

There is a well-known association between ovarian tumours and immune-mediated N-methyl-D-aspartate receptor (NMDA) receptor encephalitis associated with antibodies to those receptors in the blood and/or CSF. This is classically a subacute limbic encephalitis with clinical manifestations including prominent buccal and upper limb movement disorder and disturbance of mood and behaviour. The symptoms can respond to resection of the underlying tumour or to immune-suppression. Recovery can be complete if treatment is given early (see Chapter 12). A high proportion of those patients that are prepubertal do not have an underlying tumour. Paraneoplastic neuropathy and cerebellar syndromes are described in lymphoma but are rare in childhood (see below).

LIPOMAS

INCIDENCE AND PATHOBIOLOGY

Lipomas are space-occupying lesions of malformative origin that do not behave as tumours but small, asymptomatic lipomas, particularly in the pineal region, are now increasingly coming to light as incidental findings on cranial imaging (Spallone and Pitskhelauri 2004). The most frequent location of lipomas is the region of the corpus callosum and the quadrigeminal cistern (Gomez-Gosalvez et al. 2003; Yilmaz et al. 2006). The diagnosis is readily made by demonstrating the presence of a mass of fat density, sometimes surrounded by ‘eggshell’ calcification. Lipomas may be associated with total or partial agenesis of the callosal commissure and may communicate through a narrow stalk with an extracranial lipoma in the region of the bregma. They should be distinguished, by using MRI pre-operatively, from dermoid cysts of the anterior fontanelle (Aslan et al. 2004), encephaloceles, haemangiomas, lipomas, lymphangiomas and sinus pericranii (extracranial varicoceles).

CLINICAL FEATURES, IMAGING AND TREATMENT

Lipomas of the corpus callosum are often asymptomatic and usually do not require any treatment. Epilepsy is the most frequent manifestation of symptomatic lesions.

INTRACRANIAL CYSTS AND OTHER MASS LESIONS

The term cyst is loosely applied to a large number of intracranial cavities of multiple pathology and aetiologies such as anoxic necrosis, post-haemorrhagic lesions, vascular accidents, tumours, infections and infestations, and neurodegenerative diseases. Cysts may be of any size from huge lesions to very small, often transient and usually insignificant formations such as subependymal or frontal horn cysts in neonates (Chang et al. 2006). Some rare cystic formations may raise diagnostic problems; for example, rare cases of massive dilatation of the Virchow–Robin spaces whose significance is not fully understood (Rohlfs et al. 2005). This section considers only large primary cysts.

ARACHNOID CYSTS

Most large intracranial cysts are arachnoid cysts. The term designates fluid-filled cavities that develop either within a duplication of the arachnoid membrane or between the arachnoid and the pia mater (Gosalakkal 2002). Arachnoid cysts represent 1% of space-occupying lesions and 60–90% of symptomatic lesions are recognised during childhood or adolescence. Cysts may be an incidental finding in up to 5% of cases in autopsy studies. Arachnoid cysts are most usually malformations and only rarely follow arachnoiditis. Familial cases are rare and causes generally remain obscure (Arriola et al. 2005). Arachnoid cysts may or may not communicate with the subarachnoid space, whether located supratentorially or infratentorially.

SUPRATENTORIAL ARACHNOID CYSTS

These are the most common type of intracranial cysts. Middle fossa (sylvian) arachnoid cysts have the highest frequency in most series, followed by suprasellar cysts and cysts of the cerebral convexity. Middle fossa cysts are frequently asymptomatic and may be discovered incidentally on cranial imaging performed for various reasons (Fig. 14.23). They may be very large, pushing back the temporal lobe, which is compressed rather than atrophic. When of moderate size and found in later childhood or adolescence, these cysts may not require treatment. The most common clinical manifestations are a large head and temporal bossing. However, some reports challenge the benign nature of these cysts, describing resolution of functional neurological deficits (e.g. difficulties with atten-
tional or language skills) occurring after surgical treatment, as also described in adults (Raeder et al. 2005). Surgery is only clearly indicated when symptoms of raised ICP (e.g. headache) are present and in large cysts.

Symptomatic sylvian cysts can give rise to signs of increased pressure, especially headache and papilloedema, or to seizures, usually focal, or become manifest as a result of haemorrhagic complications. These include haemorrhage into the cyst, which may render the cavity invisible on CT, and subdural haematoma with or without associated intracystic haemorrhage. It seems likely that the 'juvenile relapsing subdural haematoma', characterised radiologically by bony changes similar to those of sylvian cysts, is a haematoma complicating a middle fossa cyst. Subdural haematoma may rarely be on the side opposite to the cyst. No treatment is ever indicated in such cases.

The diagnosis of temporal arachnoid cysts is generally easy. Large porencephalic lesions of the temporal pole may superficially mimic arachnoid cysts. Bilateral cysts of the temporal fossa have been reported in children with glutaric aciduria type I but these are also reported as atrophy of the temporal lobe, a term that seems more appropriate than that of cyst, and are not an indication for surgery.

Treatment of a sylvian cyst is best performed by fenestration into the basal cisterns either via an endoscopic approach or an open microsurgical approach. Cystoperitoneal shunting is occasionally required if there is no easy access to the basal cisterns. Drainage of huge cysts in children with closed fontanelles should be cautious as rapid decompression can produce mass brain displacement. It is not indicated for small asymptomatic cases, which are common.

Suprasellar cysts are manifested by hydrocephalus in 90% of cases. Visual abnormalities and ataxia are observed in a quarter of the cases. In some patients they are responsible for a slow anteroposterior to-and-fro movement of the head at a rhythm of 2–3Hz, known as the ‘bobble-head doll syndrome’. Partial hypopituitarism with especial involvement of corticotropin secretion is seen in 10% of patients. The full spectrum of endocrinological disturbances may also include precocious puberty and growth hormone deficiency.

The CT or MRI appearance is typical with a large rounded suprasellar mass of fluid density obstructing the foramina of Monro with resulting hydrocephalus (Fig. 14.24). MRI may show that the cyst and the third ventricle are distinct cavities separated by a thin membrane. Treatment may be with endoscopic fenestration of the cyst into the ventricle and then into the preponine cistern (Decq et al. 1996).

Arachnoid cysts of the convexity can produce focal signs and raised ICP. Interhemispheric cysts may be difficult to separate from dorsal cysts associated with agenesis of the corpus callosum. Cysts in this location are apt to be dysembryoplastic with cuboid or columnar epithelium rather than arachnoidal cells.
OTHER INTRACRANIAL CYSTS

Dermoid cysts are apt to be found in the sagittal plane of the skull. Dermoid and epidermoid cysts can produce compression of intracranial structures. Some of the dermoids are connected
by a tract to the skin and may give rise to infections. Imaging showing that epidermoids are well-demarcated lesions giving a high signal on T2-weighted images and on water-diffusion MRI (Hakyemez et al. 2005).

Colloid cysts of the third ventricle were discussed in the Intraventricular Tumours section.

Ependymal cysts are rare supratentorial, intracerebral or convexity lesions lined with an ependyma-like epithelium. They are most often located within the frontal lobe and may be associated with complex brain malformations. They do not communicate with the ventricles and probably arise from displaced segments of the wall of the neural tube that correspond to the sites from which the tela choroidea forms.

Huge prepontine cysts may extend from the prepontine region to the posterior and middle fossa. The lining epithelium is thought to be of respiratory origin in some cases.

Enterogenous cysts are also rare and generally found in the spine or posterior fossa but rare supratentorial cysts are on record.

Cysts of the Rathke cleft develop in the suprasellar region and may be associated with endocrine or visual abnormalities.

EMPTY SELLA SYNDROME

The empty sella syndrome is in fact a misnomer as the sella is not completely empty but contains a remnant of pituitary tissue. Although not a cystic formation it is described here as the sella turcica is ballooned and may be mistakenly considered to harbour a tumour or cyst. The aetiology of the condition is often related to raised ICP. Its frequency in childhood is unknown. In some cases the ‘empty sella’ is accompanied by visual or endocrine disturbances ranging from panhypopituitarism to precocious puberty. Visual field defects have been reported, and the condition may occur with microadenomas of the hypophysis. The syndrome may be seen in patients with pseudotumour cerebri, hydrocephalus and CSF rhinorrhoea. Empty sella in childhood may be less benign than in adults, and children with this condition require regular assessment.

**SPINAL CORD TUMOURS**

**INCIDENCE**

Spinal cord tumours in childhood are five to ten times less common than brain tumours and may present with symptoms and signs ranging from brainstem signs to systematic upset (Fig. 14.26). Tumours can arise anywhere along the spinal cord. For detailed discussion beyond the scope of this chapter, the account by Hsu and Jallo (2013) is recommended. A majority are intramedullary (i.e. intrinsic to the spinal cord). Spinal low grade gliomas are more likely to present later in childhood and adolescence.

**PATHOBIOLOGY**

Common tumour types include astrocytomas and ependymomas. Intradural extramedullary tumours include CNS metastatic deposits (for examples from PNET or intracranial PNET), primary intradural ependymomas, schwannomas, neurofibromas and meningiomas. Extradural lesions originate from bony elements, adjacent soft tissue or from the dura. Often large masses in the posterior mediastinum or the retroperitoneal region invade through the neural foramina (neuroblastoma) or directly invade the bone (sarcomas).

**CLINICAL FEATURES AND IMAGING**

Initial signs are often relatively subtle and symptoms may easily be disregarded as trivial complaints. Multiple consultations where the significance of symptoms of spinal origin are not initially appreciated engender delays. The clinical features of spinal cord compression include three groups of symptoms and signs:

1. Back pain and rigidity,
2. Signs of segmental spinal involvement, and
3. Signs resulting from interruption of long tracts within the spinal cord.

The importance of back pain and, especially, of spinal rigidity as an early symptom of tumour of the cord has long been known. Pain may have a radicular distribution but is more often diffuse and is usually predominantly nocturnal. Rigidity is frequently associated with scoliosis. Segmental weakness, hyporeflexia, sensory disturbances and atrophy can result from involvement of the central grey matter or nerve roots. Spasticity evolving into paraplegia, sphincter disturbances and sensory deficits result from long tract involvement.
Disturbances of walking with claudication and stiffness may be present long before other symptoms. The presence of a definable sensory level, which may be difficult to demonstrate in young children, indicates the upper level of compression. Bilateral pyramidal tract signs are present with Babinski sign and/or Rossolimo’s sign (flexion of the toes caused by flicking the tops of the toes from the plantar surface). Back pain in all children, and recurrent abdominal pain in some, should be seen as a potential ‘red flag’ which usually warrants urgent investigation. Initial bladder symptoms are increased urgency followed by retention or incontinence. Sphincter disturbances, especially urinary retention, indicate urgent need for decompression.

Occasionally intradural spinal cord tumours can present with communicating hydrocephalus and children with a new unexplained presentation of communicating hydrocephalus should be considered for an MRI of the spine (Mirone et al. 2011). Other atypical presentations of spinal cord tumours include scoliosis or an acute spinal syndrome mimicking acute transverse myelitis (Chapter 12). MRI should therefore be considered in all patients with a pathological scoliosis.

The diagnosis of spinal cord tumour should be quickly confirmed by MRI because sudden deterioration with complete paraplegia may occur at any time due to compromised circulation in the anterior cerebral artery and its branches. Magnetic resonance clearly demonstrates both intra and extramedullary lesions thus helping in guiding the management plan and has largely supplanted myelography. It is helpful in identifying syringomyelia associated with intramedullary tumours, however, distinguishing a tumour from an area of increased signal due to oedema, haemorrhage or inflammation can be difficult. Gadolinium enhancement helps make such distinctions, and diffusion-weighted MRI may be useful in some cases (Pui et al. 2005). Patients with syringomyelia where no cause is identifiable should have a contrasted MRI scan to exclude a small tumour that may not be easy to see on a plain MRI. CT may be required for patients with extradural tumours to ascertain whether bony destruction or spinal instability have occurred. CSF examination at lumbar puncture, part of the staging process in many paediatric CNS tumours, is contraindicated if there is a tumour compressing the spinal canal but is useful in detection of metastases in patients with PNET or ependymoma.

**Emergency presentations**

Spinal cord compression is an even more serious emergency than raised ICP, and this possibility must always be present in the mind of paediatricians, while the diagnoses of acute myelitis and of ‘hysteria’ or ‘malingering’ should never be accepted before cord compression has been clearly excluded. If a spinal tumour is diagnosed then the rate of progression of neurological signs must be kept under regular review. The nature of many children’s tumours is that they can progress rapidly. Extra-medullary tumours in particular, such as neuroblastoma, lymphoma or Ewing tumour can grow across the spinal canal in a matter of a few days or weeks. Referral, diagnostic biopsy and assessment for possible medical or surgical decompression is urgent and needs to be completed within 24–48 hours. Where spinal cord compression is identified, the use of immediate steroid medication such as dexamethasone in high dose (up to 10 mg/m²/day) in preparation for surgical decompression can be critical to the preservation of neurological function. Achieving a histological diagnosis also remains a strong priority and close collaboration with the neuro-oncology team can avert the risk of losing a histological diagnosis of lymphoma, which may melt away under the influence of steroids. The use of steroids in a lymphoma can also precipitate tumour lysis syndrome with the risk of acute renal failure.

**Risk of delay in diagnosis**

A useful review of the diagnostic and therapeutic challenges was provided by Wilne and Walker (2010). A population treated in a single Italian centre comprised 134 cases of benign or malignant spinal cord tumours, of 29 different histological types with a bimodal age-specific incidence with peaks in the first 12–18 months and in adolescence. Intramedullary tumours accounted for 34%, intradural extramedullary tumours 19% and extradural tumours accounted for 40% (of which 60% involved the vertebrae and 7.5% were paravertebral). Tumours of the cervical and dorsal cord predominated but all spinal cord levels were represented. The median time to diagnosis was 5.3 months (range 1 day to 2 years). The most progressive problems at the time of diagnosis were pain, paraparesis, spinal deformity, sphincter problems and hemiparesis (Spacca et al. 2015).

A second single institutional study from the USA reported a mean symptom duration of 7.8 months (0.25–60 months). A notable presenting feature they identified was early handedness in those aged less than 3 years. Radiographically homogenous gadolinium enhancement on MRI correlated with low grade histology (Crawford et al. 2009).

A Canadian population-based study of children aged less than 3 years reported three predominant tumour types including low grade astrocytoma (70%), primitive neuro-ectodermal tumour (15%) and rhabdoid tumour (15%). Gait disorder affected over 70% and the next commonest presentations were with developmental delay, abnormal eye movements, seizures, head tilt, vomiting and failure to thrive (Zelcer et al. 2011). Outcomes are significantly worse in malignant tumours (Zelcer et al. 2011) and with less compete tumour resections (Crawford et al. 2009).

**Extramedullary Tumours**

Approximately two-thirds of the extramedullary tumours are extradural in origin (Albanese and Platania 2002), originating from bone, soft tissue or the meninges. Neuroblastoma (Fig. 14.27) is the most frequent but other tumours of osseous or soft tissue origin also occur, including rhabdomyosarcoma, Ewing sarcoma (Uesaka et al. 2003), aneurysmal bone cysts, metastases, lymphomas (Daley et al. 2003) or bony deposits of Langerhans Cell Histiocytosis (LCH).

Intradural extramedullary tumours account for approximately 25% of cases, meningiomas being the most common
histological type followed by schwannomas (Fig. 14.28). Metastases from intracranial tumours, especially ependymomas and PNETs, are usually multiple and may be especially difficult to identify. So-called ‘sugar coating’ of the spinal cord from PNET metastases is seen.

Extramedullary tumours tend to manifest initially with unilateral pain in segmental distribution, often in association with paraesthesiae and weakness. Brown–Séquard syndrome is observed in a small proportion of children with extramedullary tumours. More commonly, there is only predominant weakness, spasticity and deep sensory loss on the side of the tumour, with more marked contralateral loss of pain and temperature sensation. Schwannomas (neurinomas) are more common than meningiomas.

Management of extramedullary tumours requires a histological diagnosis, relief of cord compression to preserve neurological function, removal of tumour if possible and securing spinal stabilisation. It is often appropriate to perform a needle biopsy in the first instance as some tumours such as neuroblastoma are best treated non-surgically. Decompression of the spinal cord and nerve roots and stabilisation may be appropriate when it is not appropriate or possible to completely resect the tumour. Other types of tumour such as Ewing sarcoma may be amenable to en bloc resection if appropriately localised and accessible. Bony destructive extradural tumours will often require instrumented stabilisation to prevent deformity or instability. This can be challenging in very young children.

There is some controversy regarding the role of surgical decompression in tumour related presentations. On the one hand, acute neurological deterioration is reversible with early decompressive surgery, which also offers the opportunity to get tissue for histological diagnosis without the need to access retroperitoneal tissues in the thorax or abdomen. Selection of tissue site for biopsy is critical, especially if it can offer decompression to prevent further progression of spinal injury associated with delayed tumour response to chemotherapy. The significant differences between the treatment programmes justifies the need for tissue for histology and cytogenetics as well as for research purposes. Osteoplastic laminotomy and postoperative replacement of lamina reduces the risk of subsequent spinal deformity linked to delamination but subsequent surgical instability is nevertheless a complication in a few cases. On the other hand, decompression may not be effective in preserving spinal cord function if the neurological injury has been present for more than 24–48 hours. In acute presentations where tissue diagnosis will be delayed for any reason and/or neurological deterioration is observed in spite of steroid therapy, vincristine and cyclophosphamide is used empirically as an interim treatment.

In all cases (except perhaps for simple biopsies) it is best practice to operate with neurophysiological monitoring including somatosensory evoked potential and motor evoked potential monitoring to identify cord compromise that may result in a functional deficit.

**INTRAMEDULLARY TUMOURS**

Intramedullary tumours are mainly represented by astrocytomas (30%) and ependymomas (60%). Gangliogliomas (Jallo et al. 2004) and haemangioblastomas, which may be part of the Von Hippel–Lindau complex, are rare in children. These tumours are often cystic and commonly extend over considerable lengths in the cervico-dorsal part of the cord. Some of them also involve the lower brainstem.

Intramedullary tumours are frequently associated with cystic cavitation of the central cord (syringomyelia), which may be difficult to differentiate from purely cystic intramedullary lesions. Their presentations are often subacute or diagnosed in patients under investigation for spinal surgery or associated with inherited predisposition states (NF2, NF1 and von Hippel–Lindau). They can produce symmetrical weakness of the limbs and are usually not associated with pain. Intramedullary tumours often do not produce a clear-cut sensory level and some of them may be surprisingly well tolerated for long periods despite a considerable extension (Fig. 14.29).

Some spinal astrocytomas may present with the clinical manifestations of raised ICP without local signs (Mirone et al. 2011). This may result from metastatic disease, meningeal fibrosis due to haemorrhage from the tumour, or decreased resorption of CSF because of its high protein content ‘clogging’ the arachnoid granulations. There are cases, however, in which papilloedema and raised pressure are not associated with ventricular dilatation.

The special features of intra-axial tumours of the cervicomedullary junction were described in the Brainstem Tumours section.
Spinal ependymomas complicating NF2 are often multiple and progressive during adolescence and adulthood. When not associated with NF2 they are uncommon and not infrequently present in the conus medullaris where they often demonstrate myxopapillary histology. The role of chemotherapy versus radiotherapy has not been studied in low grade astrocytoma. Primary chemotherapy, particularly in younger children, with vincristine carboplatin or other drug combinations are being investigated in clinical trials and in selected spinal cord cases; 70% non-progression rates and 50% response rates can be expected with all drug regimens. As in all CNS tumours, treatment selection by the neuro-oncology multidisciplinary team is the recommended approach (Walker et al. 2013).

Treatment of intramedullary tumours raises special problems (Houten and Weiner 2000). The spinal cord is highly eloquent and any injury often results in catastrophic disability. The guiding principles for the surgeon are to resect as much of the tumour as possible without causing any deterioration in neurological function. Factors to consider when determining if this is possible include the degree of neurological deficit, the location of the tumour, the presence of a syrinx, the presence or absence of a clear plane between spinal cord and tumour and the histological diagnosis. All resection should be performed with neurophysiological monitoring including somatosensory evoked potential and motor evoked potential monitoring. Prognosis is related to completeness of resection.

If removal proves impossible, decompression and irradiation may afford fairly long symptomatic relief in 30–50% of cases. Astrocytomas may be relatively well tolerated for long periods and when removable were reported to have a relatively favourable outcome in the context of a study in which overall long-term survival was around 50% (Townsend et al. 2004). Patients with malignant tumours such as glioblastomas mostly do poorly (Beyer et al. 2016). These tumours are thankfully rare. New forms of chemotherapy, especially cisplatin and vincristine, may improve the prognosis.

**OTHER SPINAL COMPRESSIONS**

In addition to CNS neoplasms, cord compression may result from leukaemic infiltration, lymphomas, arteriovenous malformations and congenital cysts (Garg and Dormans 2005). Other causes include epidural infections, traumatic or spontaneous haematoma. Spinal arachnoid cysts can produce a slowly progressive myelopathy but, in some cases, symptoms can fluctuate with time and postural changes (Maiuri et al. 2006). Spinal meningeal cysts are a rare cause of cord compression, which is accessible to effective treatment. Extradural meningeal cysts are diverticuli of the arachnoid through a dural opening, extending into the extradural space posterior to the cord. Extradural cysts may be associated with acquired lymphoedema of the lower limbs and lower lid ectropion and distichiasis (double row of eyelashes) in a dominant syndrome.

Other rare causes of spinal cord compression include chronic spinal arachnoiditis, which is a low grade inflammatory
reaction that may follow trauma, shunt procedures or infections, or be idiopathic, and congenital intraspinal lipomas or epidermoid tumours that can be a late consequence of lumbar puncture. Bony compression of the cord is occasionally seen as a result of overgrowth of the bone marrow encroaching on the spinal canal in patients with thalassaemia or, rarely, with other types of haemolytic anaemia or myelosclerosis (Ruo Redda et al. 2014).

OTHER CONDITIONS RELATED TO CNS TUMOURS

NEUROLOGICAL ASPECTS OF LEUKAEMIAS AND LYMPHOMAS

Complications of leukaemia may result from leukaemic infiltrations of the meninges, brain and cranial nerves, or may be due to haemorrhage, infections, or toxicity of treatments. Which of these is the cause is usually difficult to ascertain clinically.

Meningeal leukaemia may occur at any stage of the disease. One-third to one-half of children are in complete remission when neurological complications appear. CNS leukaemia may present with headache, vomiting and papilloedema but these have become rarer both because non-CNS manifestations of leukaemia are diagnosed earlier and because prophylactic CNS treatment at diagnosis prevents the development of CNS involvement. Leukaemic infiltration primarily affects the arachnoid, and infiltration of the brain tissue is rare. Cranial nerve palsies are frequently present. Retinal lesions including haemorrhages and white exudates sometimes occur with swelling of the disc. Paraspinal masses may rarely present with spinal and radicular compression. Seizures occur in about 10% of patients and may occur as a complication of methotrexate therapy or as a manifestation of venous sinus thrombosis, usually with additional clinical features of increased ICP (Sebire et al. 2005). Rarely, hypothalamic infiltration may lead to increased appetite and weight gain. The incidence of CNS tumours is increased by a previous history of leukaemia or lymphoma reflecting partly a genetic predisposition and partly an unwanted effect of their treatment with radio- and chemotherapy.

CT usually fails to demonstrate the leukaemic infiltrates but MRI with gadolinium enhancement may show the meningeal involvement. Intracranial haemorrhage is uncommon in acute lymphoblastic but more common in other types of leukaemia. Subdural haematoma or subarachnoid haemorrhage usually indicates a poor prognosis. The CSF typically showing an increased cell count with blast cells. Blast cells may, however, be associated with a low CSF cell count. The CSF glucose concentration is low in about 50% of affected children.

Lymphomas may be primary or occur as secondary tumours following leukaemia (Porto et al. 2005a) but are relatively rare in children. Primary non-Hodgkin lymphoma of the CNS is being recognised increasingly as a complication of HIV and AIDS.

Neurological complications of Hodgkin disease are also uncommon in children. Intracerebral deposits may give rise to focal signs, basal meningeal involvement with cranial
nerve palsies, and spinal extradural deposits that can produce paraplegia. These are usually associated with CSF abnormalities. Direct extension of visceral disease into the nervous system may produce compression of the brainstem, spinal roots or brachial plexus. Paraneoplastic manifestations include a cerebellar syndrome and a polyneuropathy but are rare in childhood.

The neurological outlook after lymphoblastic leukaemia is good. A single institutional study that interviewed children and young people at a median interval of 10.2 years after diagnosis at age 0.4–18.6 years of acute lymphoblastic leukaemia reported neurological symptoms in 83% of participating survivors but little symptom-related morbidity or impairment in health-related quality of life (Khan et al. 2014).

OPPORTUNISTIC INFECTIONS OCCURRING AS A COMPLICATION OF CENTRAL NERVOUS SYSTEM TUMOURS

These include bacterial, viral, fungal and protozoan diseases that have been described in Chapter 11. There are specific associations between these infections and immunosuppression, as a feature of leukaemia, lymphoma or treatment of CNS tumours. CNS numps infection is common. A progressive subacute form of measles encephalitis is rare but does occur in unvaccinated individuals and has a poor prognosis.

PSEUDOTUMOUR CEREBRI SYNDROME (IDIOPATHIC INTRACRANIAL HYPERTENSION)

Pseudotumour cerebri syndrome (PTCS) is synonymous with the term idiopathic intracranial hypertension (IIH) formerly referred to optimistically as ‘benign intracranial hypertension’. PTCS refers to a syndrome with raised ICP in the absence of a space-occupying lesion or apparent obstruction to CSF pathways. The diagnostic criteria, first defined 80 years ago (Dandy 1937) combine exclusion of mass lesions, cerebral venous sinus thrombosis (CVST) and other underlying causes with combinations of the cardinal features of symptoms of raised ICP, papilloedema or abducens nerve palsy, and elevated cerebrospinal fluid (CSF) opening pressure at lumbar puncture (LP). Although underlying causes, such as CVST, exclude the diagnosis, associated risk factors do not. It has been pointed out that the existence of these risk factors calls into question the designation of intracranial hypertension as ‘idiopathic’.

Visual loss is observed in about 10% of adults with the syndrome. Salman et al. (2001) found that it was also common in children, typically lasting for several months, and questioned the description of this condition as ‘benign’ applied to the condition. Other reports have also established that transient or permanent visual loss does occur in childhood (Orssaud et al. 2001). Therefore, sequential perimetry and assessments of visual acuity are in order whenever possible.

A normal MRI study must be obtained before considering the diagnosis of PTCS, as a normal CT scan may not be sufficient to exclude the diagnosis (Said and Rosman 2004). Magnetic resonance venography may demonstrate stenosis of the transverse sinus, sigmoid sinus and/or jugular veins. The syndrome occurs only in children of 2 years of age or more, after the skull has become resistant enough to require sufficiently high CSF pressure to dilate. Before this age, when the skull is more compliant, similar increases in CSF pressure result in hydrocephalus.

A revised set of criteria has been proposed (Friedman et al. 2013). The proposed revised criteria do not include symptoms of raised ICP and thus exclude all cases without papilloedema or abducens palsy, excepting those in whom specific supportive neuroradiological features are identifiable. The revised criteria comprise: signs of raised ICP (papilloedema or abducens nerve palsy), a minimum threshold pressure level above which CSF lumbar opening pressure must lie, and the absence of any other underlying diagnosis (e.g. cerebral venous thrombosis) on CNS imaging or CSF examination. This threshold CSF pressure level was set at 28cm H2O in the obese or sedated child and at 25cm H2O in all other children – somewhat higher than the previously accepted upper limit of the reference range in the healthy population.

Classification is likely to change as we begin to understand the pathobiology of obesity-related central hormonal metabolism (Batra and Sinclair 2014) that may mediate some cases of PTCS. Understanding of the potential mechanisms of PTCS of other aetiologies, however, remains poor. In particular, we now recognise a group of prepubertal children with PTCS whose clinical characteristics differ from those of post-pubertal children (Rangwala and Liu 2007) in whom such mechanisms are likely to be more important.

PTCS is rare with previous estimates of the annual incidence of 1.0–2.2 per 100 000 in adults. By far the largest study of PTCS in childhood to date is a UK national population-based survey that ascertained 185 cases and calculated an incidence (95% confidence interval) of 0.71 (0.57–0.87) per 100 000 children aged 1–16 years. Diagnostic error was minimised by verifying fundoscopic appearances with ophthalmologic review, excluding CVST by venography, and checking that the clinical diagnosis remained unchanged 12 months later. The incidence increased progressively from 0.17, to 0.75 and to 1.32 per 100 000 in the age bands 1–6, 7–11, and 12–16 years respectively (Matthews et al. 2017). For cases over the age of 6 years, incidence rates in girls were more than double those in boys and the percentage of cases that was either overweight or obese increased with age from 38% of 4–6-year-olds, to 60% of 7–11-year-olds and 86% of 12–15-year-olds. The triad of raised ICP symptoms, papilloedema and elevated CSF pressure, was seen in 83% of cases.
Deficits in vision (i.e. decreased visual acuity and/or restricted visual fields) at diagnosis were reported in 33% of the 98% of cases whose vision was assessed and accompanied by papilloedema in 54 (89%) of those with visual deficits. Specific neuroimaging features of optic nerve hydrops and empty sella turcica were identified and reported in 4% of cases. The median CSF opening pressure was 35.5 cm H₂O (range 12.0–74.0) and was found to be higher in those who were obese and those in whom the procedure of lumbar puncture was done under general anaesthesia. Retrospective application of the revised diagnostic criteria for PTCS (described above) excluded 9% of the cases included on the study's diagnostic criteria but those excluded did not differ from other cases in their associated clinical features (Matthews et al. 2016).

The study confirms the well-recognised risks of overweight, prior medical condition and use of antibiotics or other medications. It also showing that these factors are present in three-quarters of all cases and that these key factors interact with age and sex to create a risk of PTCS in obese adolescent girls 25-fold higher than that of 4–6-year-olds of healthy weight. Raised ICP is usually the consequence of increased venous pressure in the cranial venous sinuses, as occurs with dural venous thrombosis, or more remote venous obstruction of the superior vena cava. This produces an increase in the volume of the venous compartment of the brain, which explains the small size of the ventricles despite the high CSF pressure. Such increased venous volume is likely to account for a part of the increased resistance to CSF absorption because of the turgescence of the brain tissue itself (Karalacios et al. 1996).

In some patients spontaneous resolution of ICP may occur. Repeated lumbar punctures are often effective for up to a few days and are sometimes followed by resolution of the problem but cannot be repeated indefinitely. In other cases, treatment or removal of the cause can lead to disappearance of symptoms and signs. Weight loss, for example, has an impact on symptoms. Most patients, however, require and receive therapy additional to this although there is no agreement as to the most effective treatment approach (Matthews 2008).

Steroid administration (dexamethasone, 0.1–0.25mg/kg/day, or prednisone, 1mg/kg/day) is commonly used (Salman et al. 2001) and can be given as a 2-week course with rapid taper with relatively few unwanted effects. Longer-term steroids are used only as a last resort because of the frequency and severity of side effects and the benefit of short or longer-term steroids has not been fully assessed in this clinical context. Acetazolamide (30–100mg/kg/day) and furosemide (1–2mg/kg t.i.d.) have been found useful in significantly lowering ICP in a series of cases with no comparison group (Schoeman 1994). A lumbo-peritoneal shunt may be necessary when vision appears threatened but often requires revision and may become infected. Optic nerve fenestration may be indicated when there is evidence of progressive optic neuropathy despite therapy. Jugular venous stenting is a radiological procedure that may have a role in managing this condition.


Chapter 14  Tumours of the Central Nervous System, Other Space-Occupying Lesions and Pseudotumour Cerebri


Wells EM, Khademian ZP, Walsh KS, et al. (2010) Postoperative cerebellar mutism syndrome following treatment of medulloblas-


Yariz N, Yavuz MN, Reis A, et al. (2004) Primary cerebral neuroblas-
toma: a case treated with adjuvant chemotherapy and radiother-


# Cerebrovascular Disorders

*Gabrielle deVeber and Adam Kirton*

## Incidence and Burden of Cerebrovascular Disorders

### Arterial Ischaemic Stroke

- Anatomy, Physiology and Pathobiology in Arterial Ischaemic Stroke
- Clinical Presentation in Arterial Ischaemic Stroke
- Diagnosis in Arterial Ischaemic Stroke
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  - Conventional angiography in AIS
- Risk Factors and Causation of Arterial Ischaemic Stroke
  - Arteriopathies as a Cause of AIS
    - Focal or Transient Cerebral Arteriopathy: Inflammation, Infection or Other?
    - Dissection and Injury
    - Moyamoya Disease
  - Cardiac Causes of AIS
  - Prothrombotic and Haematological Disorders Causing AIS
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- Anatomy, Physiology and Pathobiology of Haemorrhagic Stroke
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  - Vein of Galen Malformations
Cerebrovascular Disorders

Gabrielle deVeber and Adam Kirton

Cerebrovascular disorders injure the developing brain, typically by causing stroke, focal brain damage resulting from the occlusion or rupture of cerebral arteries or veins. Two main ischaemic stroke types are arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT). In AIS occlusion of cerebral arteries, usually secondary to thromboembolism, results in focal brain infarction in a recognisable arterial territory. In CSVT thrombosis of cerebral veins and/or dural venous sinuses occurs and may or may not result in venous brain infarction. In contrast, haemorrhagic strokes involve vascular rupture and are usually subclassified by intracranial compartment (ventricular, parenchymal, subarachnoid, subdural). Ischaemic and haemorrhagic strokes are not mutually exclusive and co-occur in some cerebrovascular diseases; related conditions are covered elsewhere including perinatal stroke, preterm vascular disease, global hypoxic-ischaemic brain injuries in neonates and children (Chapters 1 and 2), as well as traumatic or extra-axial intracranial haemorrhage (Chapter 13).

For this chapter we will define stroke as a focal, vascular disorder occurring in children past the newborn period. The aim is to provide a thorough, clinically-relevant summary of current knowledge informing the care of children with stroke. An evidence-based approach is derived from our review of the literature to June 2014; while growth in childhood stroke research has accelerated in recent years, a paucity of clinical trials persists. We have drawn upon the relevant adult stroke evidence where appropriate, allowing for fundamental differences in the pathophysiology, risk factors, presentations, diagnosis, treatment and outcomes of stroke in children.

Incidence and Burden of Cerebrovascular Disorders

Incidence rates for pediatric stroke are well defined and may be increasing (Lynch et al. 2002; Mallick and O’Callaghan 2009; Tuckuviene et al. 2011). Across multiple incidence studies, there is a wide variability in age ranges, disease definitions (e.g. AIS, CSVT, haemorrhage) and study methods including case validation and reliance upon ICD coding or other administrative data. However, these studies show general agreement with the most recent and robust studies (Agrawal et al. 2009).

Original combined US ischaemic and haemorrhagic pediatric stroke rates of 2.5–2.7/100 000 children/year (Schoenberg et al. 1978; Broderick et al. 1993) are consistent with more recent studies (Fullerton et al. 2003; Agrawal et al. 2009). A recent population-based UK childhood AIS study confirmed a similar incidence of 1.6 per 100 000 and suggested increased risk for Asian and black children (Mallick et al. 2014). The prospective, population-based Canadian Pediatric Ischaemic Stroke Registry estimated combined AIS and CSVT incidence at 2.2/100 000 (1.8 AIS, 0.4 for CSVT) while a population-based Danish study found rates of 1.33 and 0.25 per 100 000 for AIS and CSVT respectively (Tuckuviene et al. 2011). Rarely, studies have suggested rates as high as 10–13 per 100 000 (Giroud et al. 1995; Lynch et al. 2002). An Australian study estimated childhood CSVT incidence at 0.34 per 100 000 children per year (Barnes et al. 2004).

Relative proportions for ischaemic and haemorrhagic strokes in childhood have been less consistent. Some studies report more haemorrhage while others report more ischaemic, suggesting proportions are likely to be equal (Earley et al. 1998; Fullerton et al. 2003). Multiple international studies suggest pediatric stroke rates are increasing (Tuckuviene et al. 2011; Gandhi et al. 2012). Factors possibly explaining an increased incidence include increased availability of sensitive diagnostic tests (MRI) and increased survival in children with at-risk conditions such as congenital heart disease, sickle cell disease and childhood cancers.

The burden of childhood stroke is large, given the substantial prevalence and long-term neurological morbidity in most survivors: compared to adults these consequences are amplified by the decades-long duration of adverse outcomes. Rates of stroke in the young (under 40) appear to be increasing (Kissela et al. 2012) and 20–25% of such individuals are children. Administrative data suggests cerebrovascular disorders are among the top ten causes of death in children (Murphy 2000) although stroke related mortality in young children may be decreasing (Fullerton et al. 2003). Economic costs of childhood stroke are substantial including for the acute and post-discharge timeframes (Lo et al. 2008) while long-term costs are less studied but likely to be substantial. Individualised attributable socioeconomic burdens may be compared to adult stroke when factoring lifelong adverse outcomes in children (Taylor et al. 1996).
which currently occupies -3% of healthcare expenditures in high income nations. Pediatric stroke is a global problem as demonstrated by evolving international pediatric stroke research initiatives.

**ARTERIAL ISCHAEMIC STROKE**

**Anatomy, Physiology and Pathobiology in Arterial Ischaemic Stroke**

Arterial blood reaches the brain via two main arterial systems. The anterior circulation originates from the internal carotid arteries (the ‘carotid system’) while the posterior circulation arises from the vertebral arteries that fuse to form the basilar artery (the ‘vertebrobasilar system’); anterior and posterior communicating arteries bridge these systems to form the Circle of Willis. Paired anterior, middle and posterior cerebral arteries arise from the circle. Anatomical flow dynamics favouring embolism into the left middle cerebral artery (MCA) may explain the left hemisphere predominance of AIS. Perforating arteries originating from the proximal portions of the paired anterior cerebral artery (ACA), MCA and posterior cerebral artery (PCA) vessels including the anterior lenticulostriate and posterior thalamostriate vessels, supply the basal ganglia and thalamus. Posterior fossa circulation arising from the vertebra-basilar arteries includes small perforating arteries supplying the brainstem and medium sized branches supplying the cerebellum (posterior inferior, anterior inferior and superior cerebellar arteries). Variable anastomoses between these arterial beds including distal leptomeningial collaterals may provide circulatory redundancy to support regional brain perfusion during reduced supply. Recognition of these watershed territories can be key in differentiating focal vaso-occlusive stroke from global hypoperfusion with focal watershed injury. Interindividual variability in cerebrovascular anatomy includes various hypoplastic segments and other congenital variations that may be clinically relevant.

Consistent with this anatomical arrangement AIS patterns are often classified as large or small vessel, based on their location within arterial territories. Occlusion of large arteries typically results in wedge-shaped lesions involving the cortex and adjacent white matter in predictable patterns. The MCA carries the largest proportion of blood flow and is most often involved in AIS. Segmental patterns of MCA occlusion are recognisable and include proximal M1 occlusion (complete loss of entire MCA territory), trunk occlusions (loss of anterior or posterior branches with sparing of basal ganglia) or lenticulostriate lesions affecting basal ganglia. Posterior circulation AIS patterns include selective regions of the brainstem, cerebellum, thalamus, occipital and temporal lobes. Recognition of arterial patterns facilitates estimation of aetiology in certain arteriopathies (Chabrier et al. 1998; Asklan et al. 2001; Braun et al. 2009).

The focal ischaemic injury of AIS typically involves thrombotic arterial occlusion. Thrombi may arrive from a distal embolic source or form locally within cerebral arteries. Regional thrombosis may result from local arterial diseases (e.g. inflammation), blood disorders (e.g. prothrombotic state), abnormal blood flow (e.g. high grade stenosis) or some combination of these factors. Thrombotic arterial occlusion may be amplified by endothelial dysfunction which has recently been implicated in childhood AIS (Eleftheriou et al. 2012). In addition, abnormalities in the hemostatic system including coagulation, fibrinolytic and/or platelet systems can predispose to thrombus formation. In contrast to slow flow venous systems where the coagulation system may predominate platelet activation with platelet-rich thrombi may be a more significant contributor to thrombosis in high flow arterial systems. It is difficult to determine which system predominates and may relate to many variables including flow rates, shear stresses, disrupted endothelium and circulating anticoagulants.

Arterial wall disease may facilitate pathological thrombosis via multiple mechanisms. In-situ cerebral arterial occlusion mechanisms include regional arteriopathies such as vasculitis and dissection. In an injured, inflamed or otherwise diseased arterial wall the normal anticoagulant functions of the endothelium are compromised and exposure of flowing blood to collagen and tissue factor occurs, activating both platelets and fibrin formation. Rapid arterial blood flow subjects the arterial wall to increased shear forces also favouring platelet activation: blood stasis or slow flow, such as arterial occlusions or severe stenoses, may favour coagulation system activation. Although precise mechanisms are incompletely understood in childhood stroke, both coagulation- and platelet-mediated thrombotic processes are important and likely to coexist. Important developmental differences in both systems may also be important (Roschitz et al. 2001; Monagle et al. 2006).

Emboli causing AIS are thrombi from the heart or proximal arteries, so-called artery-to-artery thromboembolism. Thromboemboli can also originate in the venous circulation, reaching the brain via leftward intra-cardiac shunts as seen in complex congenital heart lesions. Shunts usually moving left to right may reverse flow direction with changes in intra-thoracic pressure (e.g. Valsalva manoeuvre), resulting in paradoxical embolism. Non-thrombotic embolisation may also occur including infectious endocarditis, atrial myxomas or fragments of material from intravascular medical devices.

Brain damage from focal ischemia may depend on many factors including degree and duration of ischemia timing of reperfusion, collateral blood supply, location, developmental maturational status, metabolic demands and comorbid factors. As blood flow drops ischaemic neuronal dysfunction
occurs but can still be reversible. In transient ischaemic attacks (TIA) drops in blood flow are mild and/or brief enough to avoid permanent damage as defined by absence of lesions on MRI (Albers et al. 2002). In contrast AIS is accompanied by areas of irreversible tissue damage correlating to radiographic confirmation of infarction, however, pathological processes at the cellular level are more complex. A central core zone of permanently infarcted brain is surrounded by a penumbral zone with borderline perfusion containing potentially salvageable tissue. Factors increasing the permanent infarct volume do so by reducing penumbral perfusion or increasing metabolic demand: these include hypotension, hyperthermia, abnormal glucose or seizures. The vulnerable penumbral tissue is the primary target of acute stroke therapy and management.

Focal ischemia leads to regional hypoxia and depletion of high-energy compounds in brain parenchyma. Cerebral perfusion is dictated by mean arterial pressure, intracranial pressure and vascular resistance. Cerebral blood flow (CBF) in adults is ~ 50mL/100g brain tissue/minute while values for neonates and young children are approximately 20 and 30–50 respectively. CBF increases for children aged 3 to 10 years (~ 100mL/mg/min) before reaching adult levels by late adolescence. CBF represents 10–20% of cardiac output in infants and adults with a developmental peak >50% in infancy (Wintermark et al. 2004). Autoregulation adjusts cerebral resistance vessels in response to altered flow, carbon dioxide and metabolic factors to maintain perfusion. Cerebral autoregulation is present by term birth but matures through adolescence and may impact regional perfusion in ischaemic stroke.

Depletion of oxygen and glucose rapidly results in neuronal dysfunction with a corresponding shift from oxidative metabolism to glycolysis. Lactate production and acidosis may then further exacerbate injury. Ischaemic brain cell death evolves via two primary mechanisms. Acute necrosis occurs over hours while apoptosis evolves over days or weeks. In paediatric patients with stroke post-mortem tissue analysis has demonstrated that the duration of stroke-induced apoptosis lasts days or longer than adults. Cellular mechanisms are described elsewhere but major components include glutamate excess and receptor activation, calcium-mediated intra-cellular events, nitric oxide and free-radical generation and neuroinflammatory processes likely to also be important (Askalan et al. 2002; Shah et al. 2009). Pharmacological and neuroprotective strategies targeting these mechanisms, while successful in animal models, have been generally unsuccessful in humans. With the exception of hypothermia for neonatal global hypoxic-ischaemic injury none have focused on the developing brain where a paucity of animal models further complicate the development of neuroprotective strategies in paediatric stroke.

**Clinical Presentation in Arterial Ischaemic Stroke**

Diagnosis of stroke in children requires a high index of suspicion. Delays in AIS diagnosis are common and prolonged, often more than 24 hours from initial symptoms (Gabis et al. 2002; Hartman et al. 2009; Srinivasan et al. 2009). Children with acute neurological deficits are usually quickly brought to medical care and the largest component of time delays occur in hospital (Rafay et al. 2009). Factors influencing poor early recognition include lack of awareness by health care professionals, complex neurological symptomology and physical signs, limitations of focal neurological examination in young children, limited access to urgent specific imaging options and a broad differential diagnosis with distracting signs and symptoms (Mackay et al. 2014). Early diagnosis is required to optimise opportunities for acute neuroprotective strategies and initiation of antithrombotic therapies to promote recanalisation and prevent recurrence.

Acute onset of a focal neurological deficit is stroke until proven otherwise. In children, sudden onset of hemiparesis is the most common presenting deficit but carries a broad differential diagnosis with stroke mimics including migraine, seizure (Todd’s paresis), infections and demyelination (Shellhaas et al. 2006; Mackay et al. 2014). Other focal neurological deficits include hemianopsia, gaze abnormalities, diplopia, dysphasia, dysarthria, vertigo, nystagmus, ataxia, hemisensory changes and neglect. Stroke syndromes – a constellation of deficits localising to a specific arterial territory – are recognisable but more challenging in younger children in whom the immature brain may not yet manifest certain deficits. Seizures at stroke onset are more common in children compared with adults (Trescher 1992; Delsing et al. 2001). Non-focal neurological signs and symptoms including headache, irritability and behavioural changes are frequent present and potentially misleading (Mackay et al. 2014).

A thorough history, careful examination and judicious use of imaging and ancillary investigations are required to distinguish stroke from the complex differential of stroke mimics (Table 15.1). Adult stroke screening tools may be applicable to children but are likely to require modifications (Yock-Corales et al. 2011). Stroke signs typically begin suddenly with maximal severity at onset although fluctuations and stuttering also occurs. TIAs are not well studied in children: TIA can be defined as ‘a brief episode of neurological dysfunction caused by focal brain ischemia, with clinical symptoms typically lasting less than one hour, and without imaging (MRI) evidence of acute infarction’ (Albers et al. 2002). A recent administrative data study suggests perhaps half of children with TIA have associated stroke risk factors (Adil et al. 2014). Recognition of TIA is essential to minimise subsequent stroke occurrence.

Clinical elucidation of cause rests on a focused history and examination supported by specific imaging and laboratory investigations. Key historical variables include defining the time of onset and when the child was last seen well, the nature and evolution of current neurological symptoms and any past history of the same. History of recent infection or head or neck trauma including chiropractic neck manipulation should be sought. Relevant past history includes any chronic diseases, especially cardiac, malignancy (including cranial irradiation), child or
family history of migraine and immunisation status including varicella. Medications of interest include oral contraceptives, chemotherapy, sympathomimetics or illicit drugs. Family history screening includes thrombotic diseases, young stroke or heart attack (<50 years), as well as use of anticoagulants.

A complete neurological examination should focus on the presenting complaints while considering the age and cognitive state of the child. The Paediatric NIH Stroke Scale (PedNIHSS) is a validated, age-adjusted tool that rapidly and accurately quantifies stroke severity in children (Ichord et al. 2011). Key additional examination elements include a focused cardiovascular evaluation with blood pressure, peripheral pulses and craniofacial auscultation for bruits. Fundoscopy findings might include arterial changes or papilloedema. Hypertension may suggest renal artery involvement with fibromuscular dysplasia or moyamoya disease (Kirton et al. 2013) while skin examination could reveal PHACES syndrome, neurofibromatosis or Fabry disease.

### Table 15.1 Differential diagnosis of stroke-like episodes in children

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical distinction from stroke</th>
<th>Imaging distinction from stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Evolving or 'marching' symptoms, short duration, complete resolution, headache, personal or family history of migraine</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Seizure</td>
<td>Positive &gt; negative symptoms Todd’s paralysis is prominent and limited Altered level of consciousness</td>
<td>May identify source of focal seizures</td>
</tr>
<tr>
<td>Infection</td>
<td>Fever, encephalopathy, gradual onset, meningismus</td>
<td>Markers of encephalitis cerebritis Typically diffuse and bilateral</td>
</tr>
<tr>
<td>Demyelination (ADEM, MS)</td>
<td>Gradual onset, multifocal symptoms, encephalopathy Past history of DM events (optic neuritis, transverse myelitis)</td>
<td>Multifocal lesions, typical appearance (e.g. patchy in ADEM, ovoid in MS), typical locations (e.g. pericallosal in MS), less likely to show restricted diffusion</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Risk factor (e.g. insulin therapy), related to meals, additional neuroglycopenic symptoms</td>
<td>Bilateral, symmetrical May see restricted diffusion Posterior dominant pattern (neonates)</td>
</tr>
<tr>
<td>Watershed HIE</td>
<td>Risk factor (e.g. hypotension, sepsis), bilateral deficits</td>
<td>Bilateral, symmetrical restricted diffusion in arterial border zones</td>
</tr>
<tr>
<td>Inborn errors of metabolism (MELAS, mito)</td>
<td>Pre-existing delays/regression, multisystem disease, abnormal biochemical profiles</td>
<td>Possible restricted diffusion but often bilateral, not within arterial territories MRI spectroscopy (e.g. high lactate)</td>
</tr>
<tr>
<td>Hypertensive encephalopathy (PRES)</td>
<td>Documented hypertension, bilateral visual symptoms, encephalopathy</td>
<td>Posterior dominant, bilateral, patchy lesions involving grey and white matter, usually no restricted diffusion</td>
</tr>
<tr>
<td>Vestibulopathy</td>
<td>Symptoms limited to vertigo Positional Nystagmus</td>
<td>Normal</td>
</tr>
<tr>
<td>Acute cerebellar ataxia</td>
<td>Gradual onset, bilateral, symmetric ataxia, post-viral</td>
<td>Normal or diffusely swollen cerebellum</td>
</tr>
<tr>
<td>Channelopathies (AHC, EA, FHM)</td>
<td>Syndromic cluster of recurring symptoms Switching sides Headaches Family history</td>
<td>Usually normal Need MRA to exclude moyamoya in AHC</td>
</tr>
</tbody>
</table>

ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis; DM, demyelination; HIE, hypoxic-ischaemic encephalopathy; ADEM, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; PRES, posterior reversible encephalopathy syndrome; AHC, alternating hemiplegia of childhood; MRA, magnetic resonance angiography; EA, episodic ataxia; FHM, familial hemiplegic migraine.

### Diagnosis in Arterial Ischaemic Stroke

#### Neuroimaging

Stroke in children is a clinical and radiographic diagnosis. Efficient use of multiple neuroimaging tools is essential to optimise timing and accuracy of diagnosis, exclude stroke mimics, identify causative mechanisms and guide management.

#### Computed tomography (CT) in AIS

The initial imaging study most often performed in childhood AIS is head CT. Practical reasons include ready availability, short scan times without need for sedation, option for vascular imaging and sensitive exclusion of emergency diagnoses (e.g. haemorrhage). However, early CT is insensitive to childhood AIS and misses the diagnosis in the majority of individuals (Srinivasan et al. 2009; Rafay et al. 2009). CT findings of AIS include focal hypodensity within an arterial territory (see Figs 15.1 and 15.2), while CT can also diagnose clinically
Figure 15.1  
**Focal, transient cerebral arteriopathy.** A 13-year-old girl collapsed in school with left-sided weakness and was transferred to the adult stroke centre within 30 minutes. (a) CT scan at 45 minutes showed loss of grey-white differentiation in the right frontal lobe and a hyperdense right internal carotid artery (ICA) (not shown) while (b) CT angiography demonstrated narrowing and irregularity of the right ICA/ middle cerebral artery (MCA). The Paediatric NIH Stroke Scale score was 14 but improved spontaneously to 4 so thrombolytics were not given. (c, diffusion-weighted image) She incurred multiple additional strokes over the next 3 days and was treated with triple antithrombotic therapy and corticosteroids; (d) possible MCA wall enhancement was seen. She then deteriorated with headache, drowsiness and right pupil dilatation. (e) CT showed large haemorrhagic transformation requiring surgical evacuation while (f) conventional angiography confirmed extensive alternating areas of stenosis and dilatation with striae in the ICA, MCA and ACA. Serial MRA showed (g1, g2) worsening from day 3 to 10 with (g3, g4) improvement at 3 weeks and 6 months. At 17, the young lady is well and applying to university.

Figure 15.2  
**Moyamoya disease.** A 2-year-old girl presented with acute left hemiplegia after 3 days of gastrointestinal illness. (a) Head CT demonstrated hypodensities in the right parietal and left frontal regions with (b, c) restricted diffusion in both on DWI and ADC. (d) FLAIR MRI demonstrated chronic, small infarcts in the watershed white matter and hyperintensity of the cerebral sulci (‘Ivy sign’). (e) MRA suggested severe stenosis or occlusion of bilateral ICA with abnormal collaterals consistent with moyamoya; (f) conventional angiography confirmed same. Bilateral encephalomysynangiosis was performed and (g) right external carotid injection angiogram 12 months later showed robust cerebral perfusion. At 5 years the child was developmentally normal with stable imaging but occasional hyperventilation-induced transient ischaemic attacks.
important intra-arterial thrombus (‘hyperdense artery sign’), haemorrhagic transformation and malignant cerebral oedema. With injection of contrast CT angiography can image major and early-order branches of the cervical and cerebral arteries with potential aetiology-specific findings (see below). Although risks are low age-related complications of radiation exposure need to be considered in children.

**Magnetic resonance imaging in AIS**

Circumstances permitting, MRI is the investigation of choice for the diagnosis and evaluation of childhood AIS and cerebrovascular disease (Muir et al. 2006). Limitations include sedation in young children, longer scan times and on rare occasions contraindications like implanted metal devices. MRI is significantly more sensitive and specific than CT in paediatric AIS, particularly for small lesions or those in the posterior fossa (Paonessa et al. 2009). Diffusion-weighted MRI (DWI) is exquisitely sensitive and highly specific for acute focal brain ischemia (see Figs 15.1, 15.2 and 15.3). Restricted diffusion with DWI hyperintensity and apparent diffusion coefficient (ADC) map hypointensity in an arterial territory confirms recent (within 7 days) AIS and may also image acute Wallerian degeneration (Domi et al. 2009). Evolution of diffusion, changing over days to weeks, assists in timing stroke occurrence: T2-weighted MRI changes appear within hours and evolve over time while blood sensitive modalities (e.g. susceptibility-weighted) may identify haemorrhagic transformation. Emerging MRI applications include cerebral perfusion and autoregulation, diffusion tensor imaging (DTI), functional MRI (fMRI) and ‘wall imaging’ to explore mechanisms of arteriopathy.

Arterial imaging of the head and neck with magnetic resonance angiography (MRA) should be considered standard in the evaluation of childhood AIS. MRA can often provide images of major first and second order cerebral and cervical arteries (see Figs 15.1, 15.2 and 15.3) but has limited resolution for smaller vessels (Ganesan et al. 1999; Tardieu and Sebire 2002). MRA can identify the distribution and character of cerebral arteriopathies, such as focal stenosis or wall irregularities in contrast to the abrupt cut-off expected with embolic occlusions. Acquired cerebral arteriopathies can be followed over time using MRA (Aviv et al. 2006). Parenchymal MRI sequences can also provide important arterial information such as presence of moyamoya collaterals, the ‘Ivy sign’ on FLAIR suggestive of impaired cerebral perfusion and fat-saturation sequences of the neck to demonstrate dissection. Relying on flow signal, time-of-flight MRA may lose accuracy in areas of turbulent flow which can mimic stenosis or occlusion. This problem may be overcome with gadolinium-enhanced MRA alternatives.

**Conventional angiography in AIS**

Non-invasive angiography with MRI and CT typically provides all required information for initial diagnosis and early management, however, more detailed vascular imaging with Conventional angiography may be required in some cases (see Figs 15.1 and 15.2). Several arteriopathies may only be definitively diagnosed by Conventional angiography including the ‘double lumen’ or intimal flap signs of dissection, the banding or ‘striae’ of transient cerebral arteriopathy (TCA) and diseases of the smaller vessels (Tan et al. 2009). Conventional angiography may still fail to diagnose small-vessel vasculitis where brain biopsy is required (Benseler et al. 2005). Moyamoya disease often requires Conventional angiography for both full characterisation of disease distribution and surgical planning, where additional external carotid system imaging is paramount (Scott and Smith 2009). Conventional angiography should be considered in children with otherwise unexplained AIS with suspicion of an arteriopathic process but inconclusive non-invasive arterial imaging with computed tomography.

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**Figure 15.3** Cardioembolic arterial ischaemic stroke. A 2-year-old boy with hypoplastic left heart syndrome was well 4 months post-surgery when he suddenly stopped talking. His parents brought him to care but nearly 24 hours passed before neurology was consulted and imaging completed (a) Diffusion MRI and (b) apparent diffusion coefficient showed restricted diffusion in the anterior division of the left middle cerebral artery, (c) FLAIR MRI confirming same as well as chronic, small strokes in the periventricular white matter on the right, (d) MRA confirmed the corresponding branch occlusion. The boy recovered his language over 4–6 months and now speaks normally 3 years later. He has had no stroke recurrence on warfarin.
angiography (CTA) or MRA. In experienced hands the risk of CAs in children appears to be very low with complication rates <0.5% (Wolfe et al. 2009).

**RISK FACTORS AND CAUSATION OF ARTERIAL ISCHAEMIC STROKE**

Definitive causative mechanisms are poorly understood in childhood stroke. However, many associations have been described, typically considered as ‘risk factors’, some of which satisfy accepted causation criteria with strong biological plausibility and substantial evidence, including case-control and large population-based studies: these include complex congenital heart disease or bacterial meningitis. However, additional associations carry weaker evidence and should not necessarily be considered independently causative. In contrast to adults, stroke risk factors promoting atherosclerosis are not prominent in children: thorough and prompt evaluation of potential AIS mechanisms is essential to determine best management and optimise stroke prevention, with an approach to categorising childhood AIS aetiologies provided in Table 15.2. The following provides a review of childhood AIS risk factors weighted on incidence and evidence and as best possible.

In many children AIS remains idiopathic despite thorough investigation. In single centre studies one possible risk factor is definable in >80% of individuals (Chabrier et al. 2000; deVéber and Canadian Paediatric Ischaemic Stroke Study Group 2000; Lanthier et al. 2000; Ganesan et al. 2003). About half of children with AIS are previously healthy (Ganesan et al. 2003), with the remainder harbouring multiple potential risk factors: therefore, complete evaluations are required even when one factor is found. Risk factors for older adults are uncommon in children including atrial fibrillation and conditions associated with atherosclerosis such as hypertension, dyslipidemia, smoking and diabetes (deVéber 2003). Three major categories of risk factors predominate: arteriopathy, cardiac and haematological.

**ARTERIOPATHIES AS A CAUSE OF AIS**

Diseases of the cerebral arteries are now recognised as the leading cause of childhood AIS. Most importantly, arteriopathies are associated with the highest rates of recurrence and poor outcome (Fullerton et al. 2007b; Goldenberg et al. 2009; Goldenberg et al. 2013). Arteriopathy is present in >50% of childhood AIS (Chabrier et al. 2000; Ganesan et al. 2003; Fullerton et al. 2007b; Amlie-Lefond et al. 2009; Braun et al. 2009; Mackay et al. 2011). The clinical importance of arteriopathy underscores the essential role of arterial imaging for accurate diagnosis and classification (Askalan et al. 2001; Strater et al. 2002; Lanthier et al. 2004; Fullerton et al. 2007; Braun et al. 2009).

Different terminologies and classification schemes have been proposed for childhood cerebral arteriopathies (Sebire et al. 2004). Historical classifications suffer from a limited understanding of disease biology and variable usage of descriptors for possible mechanisms, imaging features and evolution over time. The result is a continued lack of consensus within the paediatric stroke community on how to best categorise arteriopathy to facilitate both research and clinical management (Mineyko and Kirton 2013): fortunately, improved classifications are in development (Bernard et al. 2012). Within these limitations three primary categories of arteriopathy are reviewed here:

1. A syndrome of focal, unilateral and likely to be acquired arteriopathy with possible inflammatory or infectious mechanisms,
2. Arterial dissection, and

Other less common arteriopathies are listed in Table 15.2 including posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe (PHACES) syndrome, Alagille syndrome, progeria, primordial dwarfs, childhood fibromuscular dysplasia (Kirton et al. 2013) and COL4A1 mutations (van der Knaap et al. 2006).

**Focal or Transient Cerebral Arteriopathy:**

Inflammation, Infection or Other?

A cerebral arteriopathy frequently encountered in healthy young children shares distinctive features of a unilateral disorder of intracranial arteries centred at the internal carotid artery (ICA)/MCA/ACA trifurcation and featuring irregular narrowing or stenosis, often with banding or striae of the vessel wall, AIS typically involves the basal ganglia. The arteriopathy is dynamic but transient, evolving over 3–6 months to a stable residual arterial state, with an example shown in Figure 15.1. Multiple terms have been suggested for this syndrome with slight differences among them in terms of criteria, timing and suggested mechanism. Early descriptions favoured the term ‘transient cerebral arteriopathy’ (TCA) (Chabrier et al. 1998; Sebire 2006) and serial evidence since supports the time-limited, non-progressive nature the label suggests (Braun et al. 2009). As suggested in the original descriptions (Sebire et al. 2004), fewer than 5% of cases progress beyond 6 months and those that do are likely to be a different disorder, such as unilateral moyamoya (Bernard et al. 2012; Susanne Benseler and Pohl 2013).

Despite common occurrence the pathobiology of this arteriopathy is unknown. Acknowledging this uncertainty, others have suggested the more generic term of ‘focal cerebral arteriopathy’ (FCA) for such unilateral stenosing arteriopathy without evidence of an alternative mechanism (Amlie-Lefond et al. 2009). In addition, the most commonly suggested mechanism of this syndrome is vascular inflammation (e.g. primary, post- or para-infectious vasculitis) (Chabrier et al. 1998). Based on this presumption the term ‘non-progressive childhood primary angiitis of the CNS’ has
### Table 15.2 Potential risk factors for childhood arterial ischaemic stroke

<table>
<thead>
<tr>
<th>Category</th>
<th>Common/highly probable</th>
<th>Uncommon/possible/uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arteriopathy</strong></td>
<td><em>Inflammatory/para-infectious</em></td>
<td>Secondary CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Childhood primary angiitis of CNS (cPACNS)</td>
<td>SLE, PAN, IBD</td>
</tr>
<tr>
<td></td>
<td>(nonprogressive or progressive)</td>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td></td>
<td>(large vessel or small vessel)</td>
<td>Infectious: mycoplasma, toxoplasmosis, RMSF, Lyme disease, cryptococcus, chlamydia, Japanese encephalitis, coxsackie B4 and A9, influenza A, enterovirus, parvovirus B19</td>
</tr>
<tr>
<td></td>
<td>Transient cerebral arteriopathy (TCA)</td>
<td>Post radiation vasculopathy</td>
</tr>
<tr>
<td></td>
<td>Focal cerebral arteriopathy (FCA)</td>
<td>Reversible segmental cerebral vasospasm</td>
</tr>
<tr>
<td></td>
<td>Post-varicella angiopathy (PVA)</td>
<td>(RSCV, Call-Flemming syndrome)</td>
</tr>
<tr>
<td></td>
<td><em>Infectious</em></td>
<td>Genetic: COL4A1</td>
</tr>
<tr>
<td></td>
<td>Bacterial meningitis</td>
<td>CT disease (Marfan syndrome, Ehler’s-Danlos)</td>
</tr>
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<td></td>
<td>HIV</td>
<td>Pseudoxanthoma elasticum</td>
</tr>
<tr>
<td></td>
<td><em>Dissection</em></td>
<td>Congenital: PHACES, progeria, Alagille, dwarfism (MOPDII), fibromuscular dysplasias</td>
</tr>
<tr>
<td></td>
<td>Internal carotid artery</td>
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<td></td>
<td>Vertebral artery</td>
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<tr>
<td></td>
<td>Intracranial arteries</td>
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</tr>
<tr>
<td></td>
<td><em>Moyamoya disease (idiopathic)</em></td>
<td></td>
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<tr>
<td></td>
<td>Moyamoya syndrome</td>
<td></td>
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<tr>
<td></td>
<td>Neurofibromatosis-1, trisomy 21</td>
<td></td>
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<tr>
<td><strong>Cardiac</strong></td>
<td><em>Complex congenital heart disease</em></td>
<td>Cardiomyopathy, myocarditis</td>
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<tr>
<td></td>
<td>Cardiac surgery (e.g. Fontan)</td>
<td>Aortic coarctation</td>
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<td></td>
<td>Cardiac catheterisation (e.g. BAS)</td>
<td>Severe ventricular dysfunction</td>
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<tr>
<td></td>
<td><em>Bacterial endocarditis</em></td>
<td>Atrial myxoma</td>
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<td></td>
<td>Atrial septal aneurysm</td>
<td>Valvular disease (e.g. rheumatic fever)</td>
</tr>
<tr>
<td></td>
<td>Atrial septal defect?</td>
<td>Arhythmia (atrial fibrillation)</td>
</tr>
<tr>
<td></td>
<td>Patent foramen ovale?</td>
<td>ECMO</td>
</tr>
<tr>
<td></td>
<td>Venous thrombosis + right-to-left shunt</td>
<td>Cerebral angiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embolism (air, fat, amniotic fluid)</td>
</tr>
<tr>
<td><strong>Prothrombotic</strong></td>
<td>Factor V Leiden</td>
<td>MTHFR, hyperhomocysteinemia</td>
</tr>
<tr>
<td></td>
<td>Prothrombin gene 20210A</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td></td>
<td>Elevated lipoprotein (a)</td>
<td>Antithrombin III deficiency</td>
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<tr>
<td></td>
<td>Protein C deficiency</td>
<td>Factor VII/IX/XIP</td>
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<tr>
<td></td>
<td>Lupus anticoagulant</td>
<td>Plasminogen deficiency?</td>
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<tr>
<td></td>
<td>Anticardiolipin antibodies</td>
<td>Dysfibrinogenemia?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sticky platelet syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Pregnancy, puerperium</td>
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<tr>
<td><strong>Haematological</strong></td>
<td>Sickle cell disease</td>
<td>Leukaemia</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency anaemia</td>
<td>Thalassemia?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytosis? Polycythemia?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immune thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td><strong>Medications/drugs</strong></td>
<td>Oral contraceptives</td>
<td>Cocaine, methamphetanima, ecstasy</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (L-aspariginase)</td>
<td>Ergots, triptans</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Migraine</td>
<td>Metabolic syndrome: hypertension, diabetes, insulin resistance, dyslipidemia, atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>Inborn errors of metabolism: Fabry disease, homocystinemia, mitochondrial</td>
<td>Cigarette smoking, second-hand smoke</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; PAN, polyarteritis nodosum; IBD, inflammatory bowel disease; RMSF, rocky mountain spotted fever; RSCV, reversible segmental cerebral vasocostriction; MPODII, Majewski osteodysplastic primordial dwarfism II; BAS, balloon atrial septostomy; ECMO, extracorporeal membrane oxygenation; MTHFR, methylene tetrahydrofolate reductase.

Also been applied (cPACNS) (Elbers and Benseler 2008; Benseler and Pohl 2013). Other possible mechanisms for this syndrome described in the original TCA literature include intracranial dissection, a diagnosis proven for several such individuals by postmortem examination (Dlamini et al. 2011).

A more direct role of infection may also be responsible for this arteriopathy. Post-varicella angiopathy (PVA) shares all the features described in the syndrome above: based on limited studies the primary difference is a history of varicella infection in the preceding 12 months (Askalan et al. 2001; Lanthier et al. 2005). PVA typically affects the same transient, unilateral intracranial arteries with lenticulostriate basal ganglia strokes being most common (Askalan et al. 2001; Lanthier et al. 2005). Post-varicella arteriopathy occurs in adults with ophthalmic zoster (Amlic-Leford et al. 1995). Viral re-activation from the trigeminal ganglion and trigeminovascular spread to the proximal cerebral arteries may be responsible. Cerebrospinal fluid (CSF) varicella antibodies are typically...
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...normal although polymerase chain reaction (PCR) can also be positive (Gilden et al. 2009). Isolated pathological studies have demonstrated virus in affected vascular smooth muscle cells including in two 4-year-old children who died of PVA-associated stroke (Berger et al. 2000). As varicella vaccination is now routine PVA is expected to decrease and no consistent association with vaccination has been shown (Wirrell et al. 2004; Donahue et al. 2009).

A non-specific role for infection causing paediatric AIS is also becoming increasingly clear, although the causal pathway is not yet clearly related to arteriopathy. Clinical and laboratory evidence of 'recent viral infection' have long been associated with childhood AIS (Ganesan et al. 2003), with an international study of 673 AIS children associating viral upper respiratory tract infection with arteriopathy (Amlie-Lefond et al. 2009). A recent large nested case-control study found medical visits for infection in the prior month was associated with childhood AIS (Hills et al. 2012): upcoming evidence from the Vascular effects of Infection in Paediatric Stroke study (VIPS) is expected to advance understanding of this relationship (Fullerton et al. 2011). A unifying link between active or recent infection and vascular inflammation remains to be established.

Additional infections more directly lead to AIS in children. Bacterial meningitis causes both perforating artery and large-vessel diseases resulting in AIS or venous thrombosis: imaging studies have identified such vascular complications in 5–12% of children with meningitis with rates as high as 75% in young infants (Chang et al. 2003). Subarachnoid infection may result in inflammatory thrombophlebitis of neighbouring perforating arteries though late, large artery disease is also described, particularly with streptococcus pneumonia meningitis (Chang et al. 2003). The basilar distribution and chronic, progressive nature of tuberculous meningitis represents an important and aggressive cause of childhood AIS in developing countries (Springer et al. 2009), while paediatric HIV often features arteriopathy leading to ischaemic and haemorrhagic stroke (Kleinschmidt-DeMasters and Gilden 2001). More anecdotal reports have associated childhood AIS with mycoplasma, toxoplasmosis, Rocky Mountain spotted fever, Lyme disease, cryptococcus, Japanese encephalitis, coxsackie B4 and A9, influenza A, enterovirus, parvovirus B19, chlamydia and others.

Cerebral vasculitis with isolated, non-infectious arterial inflammation can clearly cause AIS in children. Patterns of such vasculitides are increasingly described with more specific diagnostic criteria proposed (Benseler and Pohl 2013); most are isolated to the central nervous system without evidence of systemic vasculitis, so-called childhood primary angiitis of CNS (cPACNS) (Benseler and Schneider 2004; Benseler et al. 2006; Elbers and Benseler 2008; Benseler and Pohl 2013). In contrast to the non-progressive TCA-like subtype of cPACNS a progressive bilateral cPACNS is typically bilateral and involves both proximal and more distal cerebral arteries.

A third form of cPACNS is limited to distal, small cerebral arteries. Such small vessel or angiography-negative cPACNS presents with progressive, multifocal small vessel disease rather than sudden large artery occlusions and generalised, insidious symptoms including headaches, school failure and beahvioural changes. MRI appearances vary widely but heterogeneous, multifocal lesions with variable diffusion and enhancement patterns are usually seen (Benseler et al. 2005, 2006; Elbers et al. 2005; Elbers and Benseler 2008): such lesions may wax and wane with disease modifying therapy. Conventional angiography is typically indicated but since usually normal brain biopsy is usually required for pathological diagnosis (Benseler et al. 2005; Aviv et al. 2006; Benseler and Pohl 2013). Although uncommon in children small vessel vasculitis may also occur secondary to other diseases such as collagen vascular diseases, systemic vasculitides and malignancies including Kawasaki disease, Henoch-Schohnlein purpura, polyarteritis nodosa, Wegener granulomatosis, systemic lupus erythematosus, Behcet syndrome and others.

Focal arteriopathies are not just intracranial. A recent series described cervical abnormalities in childhood AIS, many of which were not explained by possible dissection (Ganesan et al. 2011). Large arteries can be involved in vasculitides such as polyarteritis nodosa or Takayasu arteritis which commonly involve major aortic branches: the latter presents with absent or asymmetrical pulses, hypertension and stroke (Ringleb et al. 2005). Paediatric forms of fibromuscular dysplasia associated with stroke also feature wide-spread systemic arteriopathy (Kirton et al. 2013).

The possibility of inflammatory or infectious arteriopathy carries important treatment implications and must therefore be considered early and appropriately investigated. Diagnostic testing may include infectious studies (lumbar puncture, serology, virology, PCR) and serum markers of inflammation (ESR, CRP) or vasculitis (ANA, extractable nuclear antigens, complement, etc.). Such testing carries a very low yield in childhood AIS and negative results should not be interpreted as definitive exclusion of an inflammatory mechanism. This is particularly true in cPACNS where laboratory tests are usually negative though small vessel varieties often have mildly abnormal CSF findings (Elbers and Benseler 2008). A recent small series suggests unique inflammatory biomarkers may be seen in children with TCA/FCA arteriopathy (Mineyko et al. 2012).

Dissection and Injury

Dissection represents a disruption of arterial wall integrity, typically with formation of a subintimal hematoma. Cranio-cervical dissection may lead to AIS by multiple mechanisms including frank arterial occlusion at the dissection site by the hematoma, regional thrombosis or both. Artery-to-artery thromboembolism appears to be the predominant mechanism of AIS (Morel et al. 2012) and extension of a dissection in either direction may further exacerbate these mechanisms. Dissection probably accounts for 15–20% of childhood AIS (Fullerton et al. 2001; Chabrier et al. 2003; Rafay et al. 2006). High risk locations for extra-cranial dissection include the proximal portion and skull base regions of the ICA and the C1-C2 segment of the vertebral arteries. Intracranial dissections also occur and may mimic FCA/TCA (169) and have the
potentially added risk of subarachnoid haemorrhage (Dlamini et al. 2011). The relative proportion of intra- to extra-cranial dissections have varied across paediatric studies (Fullerton et al. 2001; Rafay et al. 2006).

Clear risk factors for dissection include trauma to the neck, spine, or retropharynx. More subtle mechanical injuries should also be considered such as external neck manipulation, extreme physical exertion or contact sports (Chabrier et al. 2003; Rafay et al. 2006), while non-accidental trauma should be considered in young children. Many paediatric dissections appear to be ‘spontaneous’ without clear history of trauma beyond normal childhood activity which may suggest inherent abnormalities in connective tissue or other arterial wall structures predisposing to dissection. Clinically evident syndromes are seldom present but in adult case-control studies histopathological abnormalities in connective tissue structure have been reported on skin biopsies in such patients. FMD may also be associated with childhood dissection (Kirton et al. 2013).

Clinical findings suggesting dissection include new head or neck pain, often beginning 7–10 days prior to stroke presentation, ipsilateral Horner syndrome or cervical bruits. Recurrence rates are substantial in childhood dissection, estimated at 20% or higher (Fullerton et al. 2001, 2007b; Chabrier et al. 2003; Rafay et al. 2006) though adult series suggest lower rates (Weimar et al. 2010). The optimal medical management of dissections is uncertain with no randomised clinical trials: current paediatric stroke guidelines suggest consideration of anticoagulation (Monagle et al. 2008, 2012; Roach et al. 2008). A recent meta-analysis in adult dissection combining data from a number of non-randomised studies found no difference between anticoagulation and antiplatelet strategies (Kennedy et al. 2012). Intracranial dissection is a relative contraindication due to risk of subarachnoid haemorrhage, with retrospective studies supporting safety of both approaches. Long-term complications of paediatric dissection including recurrence and pseudoaneurysm require additional study (Tan et al. 2009): which activities should be restricted and for how long are unclear though paediatric stroke experts are reluctant to recommend high impact activities (Bernard et al. 2007).

Trauma without dissection may also be a risk factor for childhood AIS. A history of any head and neck trauma within 12 weeks carries an odds ratio >7 for childhood AIS that is not accounted for by arterial dissection (Hills et al. 2012). Other vascular injuries causing AIS include posttrauamatic vasculopathy (Campen et al. 2012), compression of PCA (or less commonly ACA) from increased intracranial pressure and mechanical trauma from catheterisations and extracorporeal membrane oxygenation cannulation.

**Moyamoya Disease**

Moyamoya is the progressive occlusion of the cerebral arteries at the Circle of Willis with formation of abnormal collaterals producing a ‘puff of smoke’ appearance on conventional angiography (see Fig. 15.2) (Scott and Smith 2009). Distal internal carotid artery disease is most common but unilateral and posterior circulation variants are also described. Moyamoya disease was the previously idiopathic, predominantly Asian variety now increasingly linked to genetic abnormalities, most notably RNF213 (Kamada et al. 2011). Moyamoya syndrome is associated with systemic conditions including sickle cell disease, Down syndrome, neurofibromatosis type 1, posttraudamic vasculopathy, fibromuscular dysplasia and other arteriopathies (Scott and Smith 2009).

Moyamoya is not a single disease but a recognisable syndrome. Clinical presentation can include classic stroke presentations but also includes unique scenarios such as hyperventilation-induced TIA, alternating hemiplegia and progressive cognitive decline as ‘silent’ infarcts accumulate. AIS is related primarily to regional hypoperfusion, with possible thrombotic occlusion: precipitants include intercurrent illness including dehydration that cause reduced cerebral perfusion pressures. Moyamoya typically progresses slowly over time with such non-specific symptoms including headaches: recurrent AIS accumulate resulting in poor neurological outcomes (Suzuki and Kodama 1983). Onset during infancy and certain genetic abnormalities are associated with more fulminant progression (Kim et al. 2004) and artery-to-artery thromboembolic strokes also occur. Haemorrhagic stroke risk increases with age, arising from the abnormal collateral vessels and possibly predicted by the presence of microbleeds on MRI. Hypertension often occurs in moyamoya and may be a homeostatic compensatory response or relate to renal arteriopathy (Kirton et al. 2013).

MRI findings include small, multifocal AIS, typically in a ‘string of pearls’ pattern in subcortical white matter zones, small flow voids within basal ganglia and signs of pial collateralisation including the ‘Ivy sign’ on fluid attenuated inversion recovery (FLAIR) imaging. MRA carries high diagnostic value for typical moyamoya. However, on time-of-flight MRA studies show that apparently decreased calibre in distal ICA segments can be artefactual. Functional MRI cerebrovascular reserve studies can measure relative at-risk brain and guide surgical planning (Mikulis et al. 2005; Mori et al. 2009). Conventional angiography is usually required to fully define the extent of disease and plan revascularisation surgery (Fig. 15.2).

Moyamoya treatment is multifactorial. Antiplatelet agents are often employed based on a possible thrombotic component, although evidence for stroke prevention is lacking. Risks of increased haemorrhage risk over maturation should be considered. Carbonic anhydrase inhibitors such as acetazolamide have been suggested as vasodilator treatments for moyamoya (Ikezaki 2000), however, the same effect may also cause a ‘reverse Robin-Hood’ effect where healthier reactive arteries dilate and steal blood from the most vulnerable areas, leading to new stroke. Similarly, treatment of hypertension must be very cautious given high risk of drops in perfusion pressure.

Surgical revascularisation is a highly effective treatment (Scott and Smith 2009). In older children with larger caliper arteries direct procedures can be employed connecting
extracranial arteries to distal portions of intracranial vessels, usually the MCA. Indirect procedures are highly effective and likely to be safer, where approximate extracranial branches (e.g., superficial temporal artery) are transferred intracranially to overlie the ischaemic hemisphere. Angiogenesis occurs over months, resulting in neovascularisation of vulnerable areas. Encephaloduralsynangiosis (EDAS) and encephaloduralmyosynangiosis (EDMS) are popular indirect procedures. Comparative studies of different approaches have not been done, with perioperative stroke risks likely to occur 5–10% of the time (Kim et al. 2004). Younger age at onset in moyamoya may carry an increased risk of recurrent stroke and poor outcome as well as earlier surgery may be indicated (Kim et al. 2004). Success of revascularisation surgery can be evaluated with serial angiography and non-invasive imaging. A study of 143 children undergoing pial synangiosis reported >90% with symptom free survival after 5 years (Scott et al. 2004). Follow-up of direct revascularisation over decades suggests very low ischaemic recurrence rates though haemorrhage may still occur. Presence of microbleeds on MRI appears to predict moyamoya collateral haemorrhage and may influence management (Kazumata et al. 2014).

CARDIAC CAUSES OF AIS

Heart disease is associated with approximately 10–25% of childhood AIS cases (Chabrier et al. 2000; deVeber and Canadian Paediatric Ischaemic Stroke Study Group 2000; Ganesan et al. 2003; Dowling et al. 2013). AIS is usually the result of cardiogenic thromboembolism with mechanisms relating to abnormalities in heart structure, function including rhythm, valvular integrity, blood flow and viscosity and endothelium. Procedure related stroke is triggered by cardiac surgical or endovascular treatment or circulatory support devices. Recognition of multiple AIS across different arterial territories immediately suggests a proximal embolic source, usually cardiac. Prompt and thorough cardiac evaluation is required in most childhood AIS cases, with a recent international childhood AIS study finding cardiac disorders in 204/667 (30%). These consisted of congenital defects in 60%, acquired in 20%, as well as isolated patent foramen ovale in 15%. Children with cardiac AIS were younger with higher rates of multifocal stroke and haemorrhagic transformation (Dowling et al. 2013).

Children with congenital heart disease frequently harbor silent AIS visible on pre-operatively MRI (see Fig. 15.3) (Miller et al. 2004). A single centre case-control study of >5500 cardiac surgery children found a one in 200 risk of symptomatic perioperative AIS (Domi et al. 2008). Reoperation was a risk factor as was procedure type: in particular post-Fontan stroke rates are 3–19% (Barker et al. 2005) while balloon atrial septostomy is likely to carry an even higher risk (McQuillen et al. 2006). Stroke risk with cardiac catheterisation is estimated at 1 : 600–700, increasing with interventional procedures (Hamon et al. 2006). A large, single-centre, long-term follow-up study found one-third of surviving children with congenital heart disease and stroke suffered recurrence, half of whom were not on therapeutic anticoagulation at the time (Rodan et al. 2012). Factors associated with recurrence included presence of infection at the sentinel stroke, a mechanical valve, prothrombotic condition and shorter time from sentinel stroke.

Patent foramen ovale (PFO) and other atrial septal defects are controversial risk factors for young stroke and poorly studied in children. Paradoxical cerebral embolisation of venous clots can occur across right to left intracardiac shunting when right-sided intracardiac pressures rise transiently (Mas et al. 2001). PFO are common in the general population, especially children where rates are >20–25% while associations have also been reported between cryptogenic stroke and PFO in young adults (Mas et al. 2001) but not necessarily recurrent stroke, suggesting many are incidental findings. A recent randomised trial of PFO closure in young cryptogenic stroke demonstrated no benefit for preventing stroke recurrence (Furlan et al. 2012). Presence of atrial septal aneurysm or prothrombotic conditions may heighten the risk of AIS with PFO.

Acquired cardiac conditions also cause childhood AIS (Dowling et al. 2013). Infective cerebral embolism is common in endocarditis, often resulting in mycotic aneurysm. Endocarditis should be considered clinically when fever, constitutional symptoms, murmur, Janeway lesions and Roth spots are present. Multifocal microbleeds are often seen with susceptibility-weighted MRI (Klein et al. 2009), the long-term significance of which have not been determined. Viral cardiomyopathy, acquired valve disease, arrhythmia and atrial myxoma can all lead to childhood AIS (Hays et al. 2006): in children with end-stage cardiac disease ventricular assist devices have markedly increased survival, however, stroke rates approach 30% (Fraser et al. 2012).

Children with unexplained AIS require prompt cardiac investigation with careful examination, electrocardiogram and echocardiography. Trans-esophageal echocardiograms may be superior in detecting potentially treatable stroke sources in older children and adults (de Bruijn et al. 2006) but the thin chest wall of young children improves trans-thoracic sensitivity. Cardiac MRI and rhythm monitoring are poorly studied in childhood AIS. Current guidelines suggest consideration of anticoagulation therapy over antiplatelet strategies in proven or suspected cardiogenic childhood AIS (deVeber and Kirkham 2008; Roach et al. 2008; Paul Monagle et al. 2012). Predominance of coagulation system-mediated thrombosis in cardiogenic stroke favours acute anticoagulation, most often with low molecular weight heparin (LMWH).

The duration of anticoagulation requires consideration of multiple factors including status of primary risk factor (ventricular function, completeness of surgical correction), whether the AIS was procedure-related and the presence of additional risk factors such as thrombophilia, as well as others. New comprehensive guidelines for secondary stroke prevention and other thrombotic complications of congenital heart
disease are now available to support consensus across specialists and define directions for research (Giglia et al. 2013). A recent international workshop on paediatric cardiac-related stroke has created a road map for future research.

**PROTHROMBOTIC AND HAEMATOLOGICAL DISORDERS CAUSING AIS**

Abnormalities of the coagulation, fibrinolytic or platelet systems may predispose to pathological thrombus formation. Childhood stroke thrombophilia studies are challenged by developmental hemostasis, limited evidence and variable laboratory methods, however, the association between prothrombotic disorders and childhood AIS has been repeatedly demonstrated (Barnes and deVeber 2006; Mackay and Monagle 2008).

Inherited or acquired coagulation disorders are identified in 20–50% of children with AIS (deVeber et al. 1998; Barnes and deVeber 2006). A 2010 meta-analysis summarised associations with first childhood AIS and thrombophilias (Kenet et al. 2010): the highest odds ratios were for protein C deficiency (11.0/5.13–23.59), antiphospholipid antibodies or lupus anticoagulant (6.95/3.67–13.14) and lipoprotein (a) (6.53/4.46–9.55). Modest associations were noted for factor V Ledien and prothrombin gene 20210A mutations while other factors showed minimal or no association (protein S, antithrombin III, MTHFR). These studies are generally consistent with the primary studies that drove the analysis (Chan et al. 2000; Kenet et al. 2000; Strater et al. 2002; Ganesan et al. 2003; Barnes and deVeber 2006) differing slightly from a previous systematic review (Haywood et al. 2005). MTHFR mutations have unclear significance in childhood AIS since they are common in the general population. Prothrombotic states also independently increase AIS recurrence risk (Strater et al. 2002; Ganesan et al. 2006; Rodan et al. 2012) including lipoprotein and other abnormalities (Goldenberg et al. 2013). Additional prothrombotic factors of interest include abnormal levels of plasminogen, fibrinogen, plasminogen activator inhibitor (PAI), coagulation factors (VIII, IX, XI) and an increasing number of genetic polymorphisms. Studies of platelet dysfunction have been limited in childhood AIS.

Coagulation testing should be considered in all children with AIS since these disorders are common, synergistically increase AIS recurrence risk and are potentially treatable with anticoagulation. In particular, children with idiopathic AIS and those with chronic high-risk conditions such as heart disease should have thorough investigation (Rodan et al. 2012). An experienced laboratory with established age-appropriate normative values is required for accurate interpretation. Testing is typically done at diagnosis or off anticoagulants following resolution of active thrombosis: diagnosis of a pro-thrombotic disorder requires appropriate education and counseling, ideally with thrombosis experts for future prevention.

**Part VI: Tumours and Vascular Disorders**

**Sickle Cell Disease**

Sickle cell disease (SCD) increases the risk of childhood AIS 400-fold. Approximately one-quarter of SCD children incur cerebrovascular complications including large and small vessel AIS, moyamoya and haemorrhage: most strokes are ischaemic but haemorrhagic rates increase with age and mortality is substantial (Manci et al. 2003). Large vessel SCD cerebrovascular disease affects major Circle of Willis arteries in a moyamoya pattern, while extracranial carotid disease is also described. SCD also affects small caliber end arteries, leading to an accumulation of subclinical white matter injuries. Mechanisms relate primarily to vascular occlusion potentiated by abnormal flow rates, endothelial damage by sickle red cells, low hemoglobin levels, proinflammatory genetics and hypertension (DeBaun et al. 2012).

Transcranial Doppler is an effective screening test in SCD and MCA flow velocities >200 cm/s predict stroke risk, guiding primary prevention treatment (Adams et al. 1992; Adams et al. 1998). Annual TCD screening from age 3 is routine, often accompanied by serial MRI for those with neurological symptoms, previous stroke or moyamoya (Fig. 15.8). MRI detects silent infarcts while MRA can survey changes in large vessel disease (Zimmerman 2005): the STOP trial found that regular transfusions lowering hemoglobin S below 20–30% resulted in a 90% relative risk reduction in stroke and stroke recurrence for children with abnormal velocities (Adams et al. 1998). Stroke risk appears to return when transfusions are stopped (Adams and Brambilla 2005): the SWITCH trial was stopped early as a result of increased stroke risk (and no difference in iron overload) in children switched from transfusions to hydroxyurea and (Ware and Helms 2012). The effectiveness of transfusions for small vessel disease is under investigation in clinical trials but such injuries do occur despite transfusion therapy (Hulbert et al. 2011). The STOP trial has translated into better screening and fewer strokes (Fullerton et al. 2004; Armstrong-Wells et al. 2009). Transfusions remain the standard of care despite substantial morbidity to families (Roach et al. 2008; Paul Monagle et al. 2012), while the supplementary roles of antiplatelet agents, hydroxyurea and nocturnal oxygen remain to be determined. Revascularisation surgery can be effective in SCD moyamoya (Fryer et al. 2003). Lower risk cell-based transplant therapies are increasingly employed definitive treatments for SCD though long-term effects on cerebrovascular disease are not fully elucidated.

Iron deficiency anaemia has emerged as an independent, easily treatable AIS risk factor in older infants with AIS, with this association now supported by case-control evidence (Mughie et al. 2007) Iron deficiency anaemia may be present in up to 40% of childhood AIS (Ganesan et al. 2003), however, it has not been determined how such anaemia leads to AIS. A study comparing acute imaging in SCD to other anemic children found high lesion rates in the non-SCD children where iron deficiency was prominent (Dowling et al. 2012): children with low hemoglobin and microcytosis should have...
iron studies and prompt correction with supplementation or even transfusion if severe.

Additional conditions associated with childhood AIS are categorised in Table 15.2. Migraine is associated with young stroke (Bousser and Welch 2005) but true migrainous infarction diagnosed according to international headache society criteria is uncommon in children. Special treatment considerations include calcium channel blockers (e.g., flunarizine) and avoidance of vasoconstricting triptans or sympathomimetics. Reversible cerebral vasoconstriction syndrome (RCVS) is reported in children (Kirton et al. 2006) and may warrant similar treatment. Potentially treatable inborn errors of metabolism including homocystinuria. Fabry disease and mitochondrial diseases may feature stroke-like episodes as well as actual ischaemic stroke. Modifiable metabolic and lifestyle factors prominent in adult stroke such as diabetes, hypertension, dyslipidemia, smoking and obesity are less commonly addressed in childhood AIS since atherosclerosis is not a significant cause for childhood AIS, however, these factors are still of concern in some children (Ganesan et al. 2003). Medications and illicit drugs may increase AIS risk, particularly oral contraceptives.

**TREATMENT IN ARTERIAL ISCHAEMIC STROKE**

Multiple consensus-based guidelines for childhood stroke have been generated in the past decade. These include current *Chest* (Monagle et al. 2012) and the American Heart Association (AHA) (Roach et al. 2008), publications that predominantly agree with each other though content and recommendations differ in some areas. Complementary stroke best practice guidelines from organisations such as AHA and the Canadian Stroke Network, the latter including paediatric recommendations also provide guidance. The following provides a chronological overview of general management issues for childhood AIS, referencing guidelines and other supportive evidence. Discussion of long-term treatments including stroke prevention and rehabilitation follow in the Outcomes section.

**Emergent: Neuroprotection**

‘Time is brain’ certainly applies to children with stroke. Rather than a ‘magic bullet’ medication neuroprotection refers to supportive therapy to optimise survival of at risk brain tissue: principles include optimising cerebral perfusion to deliver oxygen and glucose to the penumbra and reducing neuronal metabolic demand. Though randomised trials may never exist fundamental attention to physiological variables and prompt supportive measures to correct them may ultimately improve neurological outcome. Most children require management in paediatric intensive care units (Fox et al. 2012). Once stable, children with stroke should be promptly transferred to a tertiary care paediatric centre for management, ideally one with cerebrovascular expertise: the number and capacity of such Paediatric Stroke Centres is increasing (Bernard et al. 2014).

Blood pressure and intracranial pressure determine cerebral perfusion, while maintenance of adequate systemic blood pressure is important to maintain penumbral perfusion. Optimal blood pressure values are undetermined but targeting the upper range of normal (50–95 centile) may be reasonable. Mild hypertension may be a normal auto-physiological response to brain ischemia and blood pressure can be decreased with short acting agents (e.g., labetolol) or increased with fluids andpressor agents to achieve these parameters. Low and high glucose levels are associated with worse outcome in adult stroke (Yager and Thornhill 1997) and critically ill children (Srinivasan et al. 2004) which suggests normoglycemia is optimal, however, insulin use in acute adult stroke carries complications and no paediatric studies exist. Supplemental oxygen remains controversial in adult stroke but maintenance of normal oxygenation and ventilation seems prudent. Guidelines support aggressive treatment of fever including regular antipyretics and body cooling if needed. Induced therapeutic hypothermia has not, however, been studied in childhood stroke and trials are essentially negative in paediatric traumatic brain injury (Hutchison et al. 2008) and adult stroke. Seizures commonly occur acutely in childhood AIS and are frequently subclinical (Abend et al. 2011): since these significantly increase neuronal metabolic demand and are likely to worsen brain injury in acute AIS close monitoring and active anticonvulsant treatment are recommended. Correction of severe anaemia in both sickle and non-sickle patients appears prudent.

**Emergent: Recanalisation**

A child presenting with acute stroke is a stressful medical emergency. Initial management rests on first principles including clinical assessment, airway breathing and circulatory support, and neuroprotective care. Intravenous thrombolitics and other emergency recanalisation procedures lack evidence in children and are, therefore, not recommended in current guidelines. In particular, endovascular device use is not advisable given that such devices are designed for adults and risks in children are unknown. Accordingly, the following discussion aims only to educate and in no way represents recommendations for such interventions.

Thrombolytic agents such as tissue plasminogen activator (tPA) are standard of care in adult stroke. Given within 4.5 hours, intravenous thrombolytics improve neurological outcome across a wide-range of stroke patients with a number needed to treat of 7–8 years or better balanced by a low risk of intracranial haemorrhage.

However, in children thrombolysis safety and efficacy are not known. Child-specific considerations include differences in stroke mechanisms, hemostasis and coagulation and others. An international observational study of nearly 700 children with AIS found that 2% received intravenous or intra-arterial thrombolitics (Amlie-Lefond et al. 2009) while violations of adult tPA protocols were common. Comparison of these ‘real-world’
cases to the existing case-report literature found a publication bias toward normal outcomes. An administrative data study also found low (<1%) but increasing rates of children with stroke receiving thrombolytics with haemorrhage and mortality rates comparable to adults, although stroke diagnoses were uncertain and not validated. Using adult selection criteria, up to 10% of children with stroke may be eligible for thrombolytics (Lehman et al. 2011).

Development of emergent recanalisation strategies in children faces numerous challenges. Diagnostic delays are a key barrier although hospital arrival times are often within eligible timeframes (Ichord et al. 2007). The paediatric modification of the NIH Stroke Scale (PedNIHSS) provides a quick, valid assessment of stroke severity (Ichord et al. 2011) while the Thrombolysis in Paediatric Stroke study (TIPS) was a safety and dose-finding trial of intravenous tPA within 4.5 hours in children 2–18 years of age. TIPS was recently stopped as a result of lack of recruitment but generated important data on the development of acute paediatric stroke treatment programs (Bernard et al. 2014). Potential benefits of intervention thrombolytic or mechanical therapies continue to be investigated in adult stroke while only anecdotal experience is reported in children (Amlie-Lefond et al. and Members of IPSS 2007) with additional challenges of smaller patient size and decreased availability of paediatric neurointerventional facilities and specialists. A summary of 34 published cases of endovascular paediatric AIS treatment (Ellis et al. 2011) found wide ranges of time to treatment, recanalisation rates and outcomes: among 28 with data recanalisation was either absent or only partial in over half (15) and (eight) had procedure related complications (Amlie-Lefond et al. 2007). The authors recommend that only children with severe deficits (NIH Stroke Scale > 10) be considered for treatment and then only by interventional teams with specific paediatric experience and paediatric stroke neurologists.

Urgent: Antithrombotic Therapies

Pathological thrombus is a primary therapeutic target in childhood AIS. Accordingly, antithrombotic therapies are an urgent consideration to prevent early recurrence or propagation and possibly promote recanalisation. Two strategies are typically considered early: heparins targeting the coagulation system or antithrombotic agents, typically acetylsalicylic acid (ASA). Based predominantly on theory, anticoagulation approaches are favoured for mechanisms such as cardiogenic stroke, high grade (low flow) stenosis or severe thrombophilic states while ASA may be preferred for many arteriopathies where endothelial disruption may favour platelet-rich thrombogenesis. Agent selection for other circumstances, such as dissection, remains controversial. No randomised controlled trials exist and choices of antithrombotic therapy vary widely among paediatric stroke experts (deVeber and Canadian Paediatric Ischaemic Stroke Study Group 2000; Fullerton, deVeber and IPSS investigators 2007; Goldenberg et al. 2009), with published guidelines slightly discordant (Roach et al. 2008; Monagle et al. 2012). These two approaches (antiplatelet, anticoagulant) are not mutually exclusive and may change over time as stroke mechanisms are better understood and in individuals as recurrent events necessitate. Withholding early antithrombotic treatment is not currently supported by the combination of substantial safety data for all agents and high risk of early recurrence (deVeber and Canadian Paediatric Ischaemic Stroke Study Group 2000; Strater et al. 2001).

Guidelines currently support anticoagulation as a possible first line therapy in childhood AIS (Monagle et al. 2012). An international study of 661 children found anticoagulation was consistently given to children with cardiac and dissection aetiologies (Goldenberg et al. 2009). Anticoagulation is safe in children with arteriopathy (Bernard et al. 2009) while effects of anticoagulation on haemorrhagic transformation of childhood AIS appear minimal (Beslow et al. 2011; Schechter et al. 2012): relative contraindications include intracranial haemorrhage, uncontrollable hypertension or haemorrhage diathesis. Age-dependent hemostasis differences need to be considered in young children, with duration of therapy depending on clinical indication. Two primary alternatives exist for early anticoagulation.

Unfractionated heparin (UFH) inhibits coagulation pathway enzymes. Age-specific dosing guidelines for childhood AIS range from 28 units/kg/hr in infants to adult doses of 18 units/kg/hr in older children (Monagle et al. 2012). Risks of heparin include haemorrhage and heparin-induced thrombocytopenia in <4% although rapid reversal of heparin effects with protamine may be advantageous in select circumstances. Monitoring by activated partial thromboplastin times (APTT) and heparin levels may be challenging: LMWHs are subcomponents of heparin. LMWH differences include subcutaneous dosing, more predictable pharmacokinetics, less frequent monitoring and lower risk of thrombocytopenia. These differences, and the substantial nature of childhood AIS safety data (deVeber and Canadian Paediatric Ischaemic Stroke Study Group 2000; Bernard et al. 2009) have resulted in LMWH becoming a treatment of choice at many centres for acute anticoagulation of childhood AIS. Dosing and monitoring guidelines are available (Monagle et al. 2012) and typically involve once or twice daily injections as well as monitoring of antithrombin III: levels of 2.0–3.0 (2.5–3.5 for mechanical heart valves) while relative contraindications include infants and young children with unpredictable vitamin K levels, children with gastrointestinal disorders or those playing contact sports. New oral anticoagulants currently being tested in children have not yet been evaluated for paediatric stroke prevention but appear favourable in adult populations. New guidelines for antithrombotic therapy in children with complex congenital heart disease should also be accessed (Giglia et al. 2013).
Guidelines also currently support antiplatelet agents as first line therapy for non-cardiogenic childhood AIS including headaches, while altered level of consciousness must be reacted to immediately as waiting until later signs including pupillary dilatation may reduce good outcomes. Management includes stabilisation, emergent imaging (CT) and measures to reduce intracranial pressure (sedation, paralysis, manipulation of pCO2 and osmotic therapy). Randomised trial evidence supports a net benefit of decompressive hemicraniectomy in adult stroke (Vahedi et al. 2007), while studies of malignant cerebral oedema in childhood AIS have been limited but suggest outcomes are favourable, including quality of life measures and those with dominant hemisphere lesions (Ramaswamy et al. 2008; Smith et al. 2011).

Anti-inflammatory treatment with steroids as is used for definite CNS vasculitis may have a role in transient cerebral arteriopathy with a presumed inflammatory basis. There are no definitive clinical, imaging or laboratory biomarkers to confirm active inflammation in acute unilateral arteriopathy of the TCA subtype. Steroids have modest side-effect profiles in acute stroke in adults and they may modulate the arteriopathy reducing the severity of eventual arterial stenosis and risk of early recurrent stroke: based on the natural history of TCA with stabilisation by 3 months a short course of corticosteroids could be considered (Benseler and Pohl 2013), while some evidence supports the use of such immunomodulatory therapy in small vessel cPACNS (Hutchinson et al. 2010). TCA in the context of either active varicella infection or possibly post-varicella angiopathy could warrant antiviral therapy. Additional treatments targeting adult stroke complications that should be considered in children include aspiration prevention, feeding and nutrition, skin care and deep vein thrombosis prophylaxis. The benefits for outcome facilitated by the development of stroke units in adults will hopefully be realised as more specialised paediatric stroke centres develop (Bernard et al. 2014).

**OUTCOMES AND CHRONIC MANAGEMENT IN ARTERIAL ISCHAEMIC STROKE**

Survivors of childhood stroke typically experience neurological morbidity including moderate to severe deficits or epilepsy in >50% (Ganesan et al. 2000; deVeber et al. 2000; Delsing et al. 2001) while mortality rates are 5–10% (deVeber et al. 2000; Delsing et al. 2001). Comprehensive rehabilitation targets physical, occupational, language, cognitive/behavioural and psychosocial consequences for both child and family (Paediatric Stroke Working Group 2004). Lessons from evolving evidence-based guidelines for adult stroke rehabilitation are applicable: while the ‘enhanced plasticity’ suggested to improve outcomes from early brain injury is an oversimplification age is one of many complex variables that must be considered. Evolving understanding of developmental plasticity and brain reorganisation are providing new strategies to promote recovery (Kirton 2013).

Hemiparesis and motor disabilities are a leading sequela of childhood AIS with major functional consequences (deVeber et al. 2000; Ganesan et al. 2000). The upper extremity is often most affected because of MCA involvement but leg and gait problems are also common: damage to basal ganglia or cerebellum may lead to additional movement disorders or ataxia, while post-stroke hemidystonia can emerge months after basal ganglia infarction and be disabling. Neuroimaging may allow some prediction of motor outcomes at diagnosis (Boardman et al. 2005; Domi et al. 2009) and physical as well as occupational therapies remain the mainstay to optimise motor recovery though evidence specific to childhood AIS is sparse (Dobkin 2004). Programs combining strength and aerobic conditioning, task-specific training and promotion of an active lifestyle are recommended. Constraint induced movement therapy (CIMT) pairs restraint of the unaffected limb with therapy to promote hemiparetic limb function. Evidence supports marked long-term CIMT effectiveness in adult stroke (Taub et al. 1998; Taub et al. 2002; Wölfe et al. 2006, 2008) with emerging evidence in perinatal stroke paediatric populations (Taub et al. 2004; Sung et al. 2005; Charles and Gordon 2006; Taub et al. 2007), however, trials in childhood stroke are required, while bimanual therapy approaches may compliment CIMT (Charles and Gordon 2006). Non-invasive neuromodulation such as transcranial magnetic stimulation (TMS) now has substantial randomised trial evidence in adult stroke motor rehabilitation (Hsu et al. 2012). A small randomised trial in childhood AIS demonstrating favourable tolerability and possible benefit on motor function requires replication (Kirton et al. 2008).

Peripheral electrical stimulation recommended in some adult stroke rehabilitation guidelines are untested in children, however, robot-assisted rehabilitation and virtual reality strategies being advanced in adult stroke may be applicable. Spasticity and dystonia limit function in children with AIS. Selective use of botulinum toxin can alleviate tone on chronic function though issues of cost, frequency and tolerability must be considered. Assistive devices such as ankle-foot orthoses or hand splints may facilitate positioning and function in adult stroke while in growing children with disability attention to musculoskeletal health including bone density and scoliosis is important. For all rehabilitation needs a multidisciplinary approach combining orthopaedic and physical medicine physicians, occupational, physical and speech therapists, child psychologists and educational specialists as well as other parties is required. Morbidity-targeted interventions should include objective, blinded pre- and post-interventional outcome measures focused on function and participation whenever possible.

Neuropsychological impairments limit academic success and psychosocial health (Friefeld et al. 2004; Nass and Trauner 2004). On average, children with AIS have moderately impaired global intellectual function (Hetherington et al. 2005; McLinden et al. 2007) that is difficult to predict by age,
lesion size, side or location. Verbal learning and memory are often impaired in children following stroke (Lansing et al. 2004; Max 2004; Studer et al. 2014) while language dysfunction is common (Hertz-Pannier et al. 2002) and associated with dominant hemisphere lesions (Nass and Trauner 2004). Formal neuropsychological testing is often required to optimise educational planning including serial measures as deficits may emerge across development (Westmacott et al. 2007; Westmacott et al. 2009). Potentially treatable, attention-deficit–hyperactivity disorder rates are increased (Max et al. 2004) while emotional and behavioural disorders including depression, anxiety and impaired social function may also develop (Mosch et al. 2005), impacting health-related quality of life and peer relationships (Neuner et al. 2011).

Given high recurrence rates, secondary stroke prevention is a key medical issue. Stroke and TIA recurrence risks range from 7% to 35% (deVeber et al. 2000; Lanthier et al. 2000, 2004) with population-based data suggesting 5-year rates of 20% (Fullerton et al. 2007b): risk is heavily weighted to children with arteriopathy (Chabrier et al. 2000; Lanthier et al. 2004) with rates >65% (Fullerton et al. 2007b). There are no randomised trials but observational data demonstrates recurrence rates are higher in children not on antithrombotic therapy (Lanthier et al. 2004) while ASA (1–5mg/kg/day) is most often employed (Goldenberg et al. 2009), consistent with published guidelines (Roach et al. 2008; Monagle et al. 2012): select conditions including certain cardiac conditions may indicate long-term anticoagulation (Giglia et al. 2013). Other prevention treatments include immunomodulation for vasculitis, transfusions for SCD, revascularisation surgery for moyamoya, removal of medications and treatment of medical conditions (e.g. iron deficiency). Good arterial health should be emphasised including balanced nutrition, regular exercise, avoidance of smoking and drugs, as well as surveillance for hypertension and dyslipidemia.

Remote symptomatic epilepsy occurs in 15–20% of childhood AIS survivors (deVeber et al. 2000; deVeber and Canadian Paediatric Ischaemic Stroke Study Group 2001; Fitzgerald et al. 2007). Most are focal, arising from perilobular areas, though bilateral EEG abnormalities and epileptic encephalopathies can occur (Fitzgerald et al. 2007; Kirton et al. 2008). Concerns that ongoing clinical seizures or even subclinical pathological electroencephalographic activity can adversely affect plastic neurodevelopment and recovery in children after stroke are theoretical but important: predictors of epilepsy may include cortical involvement (deVeber et al. 2000) as well as younger age and seizures at presentation and careful historical screening for seizures as well as judicious use of electroencephalography is required. Treatments follow fundamental principles of anticonvulsant use in children: as a focal injury in a previously healthy brain, children with AIS can be excellent epilepsy surgery candidates (Wyllie et al. 2007).

Headaches are more common in childhood stroke, occurring in one third of patients (deVeber et al. 2000). Risks include underlying diseases such as moyamoya, comorbid primary headache problems (e.g. migraine) as well as psychological factors. Worsening headaches may indicate disease progression or recurrence in certain disorders including cPACNS or moyamoya. Most established headache interventions are safe in children with AIS with exceptions including effects of non-steroidal anti-inflammatory medications on ASA effectiveness and vasoconstricting triptans in children with migranous infarction or other vasculopathy.

Complete psychological and social support of child and family is essential. Family-centred care allows identification of the complex psychosocial challenges faced by most families. Effects on quality of life occur in most survivors and their family (Gordon et al. 2002) and relate to both neurological and psychosocial factors (Friefeld et al. 2004). Coping strategies may improve adult stroke outcome but are unstudied in children. Treatment should consider the lifestyle of the individual child, goals and level of functioning and be integrated into the school and home environments (Paediatric Stroke Working Group 2004), while parental guilt may also be an educational target (Bemister et al. 2014). Families require guidance in interpreting the many unproven therapeutic options presented to them, including those with legitimate potential (e.g. stem cells) and none at all (Rosenbaum 2003). Educational and supportive organisations are increasing on a global scale (IAPS 2014).

**CEREBRAL SINOVENOUS THROMBOSIS**

Cerebral sinovenous thrombosis (CSVT) represents thrombosis within the cerebral venous system. Only about 50% of children will have parenchymal involvement with venous infarction, which is often haemorrhagic. Estimates of CSVT incidence range from 0.25 to one in/100,000 children/year, accounting for about 25% of paediatric ischaemic strokes (Barnes et al. 2004; Mallick and O’Callaghan 2009). In neonates, who are at greatest risk, diagnosis has improved but is often still missed (Golomb et al. 2009): evidence rests on a seminal population-based study of 160 consecutive paediatric CSVT (deVeber et al. 2001) and more recent large patient series (Heller et al. 2003; Kenet et al. 2004; Sebire et al. 2005; Jordan et al. 2010). As a treatable condition with high mortality clinical awareness of neonatal and childhood CSVT is essential.

**Anatomy, Physiology and Pathobiology of CSVT**

A network of veins and sinuses drains blood from the brain with patterns generally flowing medially towards midline channels then posteriorly. Cortical veins feed the superior
sagittal sinus in the superficial system, with internal cerebral, medullary, thalamic and other deep system veins converging at the Vein of Galen and straight sinus in the deep system: these two systems join the torcula before draining into bilateral transverse and sigmoid sinuses that empty into the internal jugular veins. Other recognisable venous territories include cavernous and petrosal sinuses, large superficial veins (e.g. Trolard, Labbe) and a venous network draining the posterior fossa. The sinuses are passive venous channels existing between layers of the dura mater. A fixed lumen allows slow, potentially reversible flow sensitive to impaired venous return. In supine infants the occipital bone may mechanically compress the superior sagittal sinus (Tan et al. 2011): as most CSF re-absorption also occurs in the sagittal sinus thrombosis or venous hypertension may result in hydrocephalus. Consideration of venous anatomy and biology allows recognition of CSVT infarction patterns: bilateral parasagittal infarcts are typical of sagittal sinus thrombosis (see Fig. 15.4). Thrombosis of the deep venous system results in oedema, infarction and haemorrhage involving thalamus, basal ganglia and deep white matter. Secondary haemorrhage into neighbouring ventricles is common (Wu et al. 2003).

Coagulation cascade activation and fibrin-rich thrombosis predominates in CSVT over platelet-mediated processes. The importance of prothrombotic conditions or states, both acquired or inherited, therefore, have greater impact. Virchow’s triad describes alterations in blood composition, flow or the vessel wall as promoters of thrombosis and provides a practical framework to consider CSVT mechanisms and risk factors. Anticoagulant mechanisms may differ in the venous system compared with the arterial system where endothelial thrombomodulin levels are increased (Lin et al. 1994): venous wall injury may relate to infection or inflammation, trauma, surgery or compression (Deitcher et al. 2004; Tan

**Figure 15.4** Cerebral sinovenous thrombosis (CSVT). A 16-year-old boy with active inflammatory bowel disease had diarrhoea, mild dehydration and iron deficiency anaemia. He presented with sudden onset left leg weakness and several days of diffuse new headache. (a) Head CT demonstrated focal hypodensity in the right frontal lobe (open arrow) and possible hyperdensity in the superior sagittal sinus (closed arrow) while (b) CT venogram confirmed multiple filling defects in the superior sagittal sinus diagnosed as CSVT; (c) MRI showed bilateral, parasagittal oedematous lesions with (d) only the inner portion having restricted diffusion. After 3 months of anticoagulation the young man had mild leg weakness with (e) full recanalisation of the venous sinuses and chronic infarcts with hemosiderin staining on MRI.
et al. 2011). Mechanisms are not mutually exclusive and many children with CSVT will harbour multiple risk factors across these elements.

CSVT obstructs venous flow, increasing venous and tissue pressure within brain parenchyma. Consequences will depend on the location and degree (complete or not) of blockage and range from focal changes in a discrete venous territory to global drainage impairment with increased intracranial pressure. Initially, increased regional tissue pressure results in vasogenic oedema, producing neurological symptoms without infarction. Variable alternative venous drainage pathways and collaterals may mitigate this process. Further increases in venous pressure will eventually exceed incoming arterial pressure leading to infarction. MRI may distinguish these states of parenchymal disease, comparing diffusion sequences to T2 (see Fig. 15.4), however, restricted diffusion lesions may sometimes reverse.

Clinical Presentations of CSVT

CSVT must be recognised quickly to minimise poor outcomes. Diagnosis is challenging, particularly in infants who account for ~50% of paediatric CSVT (Carvalho et al. 2001; deVeber et al. 2001). In contrast to AIS a gradual onset of diffuse neurological signs and symptoms is more typical: common presentations include headache, nausea and vomiting and markers of signs of increased intracranial pressure (papilloedema, VIth nerve palsy). Childhood CSVT often mimics idiopathic intracranial hypertension (IIH) while seizures are more common, compared to both childhood AIS and adult CSVT, occurring in 40–90% (deVeber et al. 2001; Wasay et al. 2008): focal deficits can occur acutely but are more common in older children (Rivkin et al. 1992; Carvalho et al. 2001; deVeber et al. 2001). In the largest published study, proportions of presenting features included headache (54%), seizure (48%), altered consciousness (49%), focal signs (53%) and papilloedema (22%) (deVeber et al. 2001).

Diagnosis of CSVT

NEUROIMAGING

Childhood CSVT diagnosis requires timely use of appropriate neuroimaging. Imaging diagnosis shares the challenging nature of clinical recognition and is often missed or delayed with many mimics and pitfalls (Shroff and deVeber 2003). Illustrative imaging-based reviews of childhood CSVT diagnostic approaches and challenges are available (Bracken et al. 2013). Parenchymal imaging can be diagnostic, however, the principal required approach involves clear imaging of the venous system to demonstrate filling defect(s). CSVT distribution ranges from diffuse major sinuses to discrete single veins: multiple sinuses or veins will be involved in about half of patients (deVeber et al. 2001) while thrombus location, extent and degree of occlusion are likely to determine parenchymal injury. Infarct patterns correlate with affected venous drainage territories in children (Tekasam et al. 2008) with the superficial system most commonly affected. Deep system CSVT is most diagnostically challenging where even a small thrombus in a critical location such as the straight sinus may have catastrophic consequences, however, modern neuroimaging has greatly improved the accuracy of childhood CSVT diagnosis.

CT without contrast cannot exclude CSVT (Bousser and Russell 1997). Focal hyperdensity of veins or sinuses can be observed but a significant false positive rate is seen, particularly in young infants with higher hematocrits, slower flow and relatively hypodense brain tissue (Davies and Slavotinek 1994). Subdural haemorrhage layering over the tentorium in young infants or trauma patients can mimic transverse sinus thrombosis. Imaging showing a hyperdense straight sinus, thalamic stroke and/or intraventricular haemorrhage are recognisable, life-threatening presentations of deep system CSVT (Linn et al. 2009). Contrast-enhanced CT venography (CTV) is a highly sensitive and specific diagnostic test for childhood CSVT: filling defects in venous structures are diagnostic and thinner slices with multiplanar reformations improve diagnostic accuracy (Figs 15.4 and 15.5) while contrast outlining luminal thrombus may result in an ‘empty delta’ sign at the torcular. Combining CT and CTV across multiple imaging intervals warrants concern given repeated radiation exposure in children.

MRI is often indicated in childhood CSVT. Advantages over CT including better assessment of brain parenchyma and lack of radiation are countered by the need for sedation in young children. MRI can differentiate venous congestion and vasogenic oedema (FLAIR sequences) from cytotoxic oedema and infarction (restricted diffusion) as well as from haemorrhagic transformation (blood-sensitive sequences) (Fig. 15.4). MRI can also characterise the extent and nature of the thrombus itself, often appearing hyperintense on T1 and T2 images (Fig. 15.6) although many mimics exist (Leach et al. 2006). Susceptibility-weighted MRI may be more sensitive for small cortical vein thromboses. Restricted diffusion of a thrombus may predict slower recanalisation (Favrole et al. 2004) (Fig. 15.6). MRI venography (MRV) is often comparable to CTV, however, with important differences: options include time-of-flight and gadolinium-enhanced venograms. Time-of-flight studies are subject to flow artifacts (Ayanzen et al. 2000) mimicking filling defects and must be interpreted with caution. Enhanced MRV appears superior to time-of-flight in adults and has similar utility in children (Farb et al. 2003). Careful interpretation is essential and CTV may be required for confirmation.

RISK FACTORS AND CAUSATION OF CSVT

Associations with reasonable biological plausibility of a causative role can be defined in most children with CSVT. Associated factors vary by age, with neonates and young infants
Cerebrovascular Disorders

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Figure 15.5  Cerebral sinovenous thrombosis (CSVT). A 6-year-old boy with vomiting and diarrhoea for 4 days due to gastroenteritis presented with new onset headaches and personality change. Examination revealed a dehydrated, encephalopathic child with papilloedema while laboratory studies found severe microcytic anaemia and iron deficiency. Head CT demonstrated (a) bifrontal hypodensities with haemorrhagic transformation and (b, arrows) CT venogram showed a large burden of thrombus throughout the superior sagittal sinus. Treatment including anticoagulation resolved the thrombosis by 3 months: at 2 years, (c) the child has extensive encephalomalacia with global delays, behavioural disorder and symptomatic epilepsy.

Figure 15.6  Cerebral sinovenous thrombosis (CSVT). A 7-year-old boy was undergoing induction chemotherapy for acute lymphoblastic leukemia including L-asparaginase. He developed recurrent, paroxysmal complex visual hallucinations and new headache. (a) MRI demonstrated hyperintense signal throughout the superior sagittal sinus (SSS) on T1 consistent with CSVT. (b) A parasagittal image demonstrated a focal lesion with restricted diffusion and subacute haemorrhage in the visual association cortex consistent with venous infarction. (c) Thrombus in the SSS and a cortical vein also demonstrated restricted diffusion.

more likely to be idiopathic. About two-thirds of children harbour multiple risk factors (deVeber et al. 2001) that combine to cause disease, suggesting a thorough evaluation is required in most patients even when one potential factor has been identified. The largest population-based study of childhood CSVT described the following proportions of risk factors: prothrombotic disorders (41%), dehydration (25%), systemic infection (9%), head and neck infection (18%), other head and neck disorders (12%), haematological disorders (12%) and malignancy (8%). Most studies to date have categorised major risk categories of infection, prothrombotic states, as well as both acute and chronic diseases.

Infection is commonly associated with childhood CSVT. Septic CSVT occurs in the context of head and neck infections including otitis media, mastoiditis, sinusitis, meningitis and others. Septic CSVT is likely to account for up to 50% of patients (deVeber et al. 2001; Sebire et al. 2005; Wasay et al. 2008): mechanisms include direct spread of infection from tissue sites into neighboring venous sinuses resulting in thrombophlebitis. In addition, infections may promote CSVT via more systemic mechanisms such as dehydration in gastroenteritis, systemic inflammatory responses and septic coagulopathy. Human necrobacillosis casues Lemierre syndrome with pharyngitis and neck pain progressing to jugular
thrombosis (Jaremko et al. 2003). Complete infectious history and focused examination for head and neck infections including ears, mastoids, sinuses and meningismus are therefore essential: complete infectious investigations, including cerebrospinal examination, are often required to inform prompt and effective treatment.

Prothrombotic disorders have long been associated with childhood CSVT, reported in 20–80% of series (Ganesan et al. 1996; deVeber et al. 1998; deVeber et al. 2001). This prevalence appears larger than adult CSVT where estimates are only 15–20%: a systematic review and metanalysis childhood CSVT patients described the following odds ratios for prothrombotic conditions: antithrombin III deficiency (18.41, 3.25–104.29), protein C deficiency (6.30/1.56–25.40), protein S deficiency (5.27/1.53–18.21) and factor V Leiden (2.74/1.73–4.34), while multiple other thrombophilias did not reach statistical significance. The largest single prospective case-control study of 149 children found coagulation abnormalities in 56% compared with 21% of controls (Heller et al. 2003). A metanalysis of genetic factors in adult CSVT confirmed associations with FVL and PTG20210A that appeared stronger than in childhood CSVT (Marjot et al. 2011). Recurrence of CSVT has been associated with prothrombotic conditions (Kenet et al. 2007) although results from the metanalysis above were inconclusive. Novel prothrombotic states associated with adult CSVT such as factor XII C46T are untested in children: D-dimers may be a serum biomarker of CSVT in adults and are currently being studied in children. Given these associations and the common occurrence of multiple risk factors a prothrombotic evaluation is typically required for children with CSVT.

Many underlying medical conditions increase the risk of CSVT. Dehydration is a common, recognisable and imminently treatable factor. Chronic systemic diseases commonly co-occur in older children with CSVT: inflammatory bowel disease (Fig. 15.4) confers multiple risks including systemic inflammation, diarrhoea-induced dehydration and iron-deficiency (Standridge and de Los 2008). Risk is increased in children with lupus anticoagulant and antiphospholipid antibodies in systemic lupus erythematosus. Malignancies and their treatment may create prothrombotic states such as chemotherapy side-effects (L-asparaginase), immunocompromised states and resultant infections, cerebral involvement of cancer and interventional procedures (Deitcher et al. 2004). CSVT may complicate 1:200 childhood acute lymphoblastic leukaemia patients (Santoro et al. 2005) while nephrotic syndrome may deplete coagulation factors to increase CSVT risk (Fluss et al. 2006).

Iron deficiency anaemia is an independent, treatable risk factor for childhood CSVT (Sebire et al. 2004; Maguire et al. 2007). Cardiac disease is present in <10% of children with CSVT and may relate to surgery, instrumentation or other factors (deVeber et al. 2001; Sebire et al. 2005). Traumatic head injury with direct damage to venous sinuses causes CSVT: of 131 children requiring CT for head injury 6% had CSVT (Stiefel et al. 2000). An all ages study of nearly 1000 patients with trauma and head CT found CSVT in >10% with risk approaching 35% when fractures approximated a sinus (Rivkin et al. 2014). Mechanical compression of the sagittal sinus in infants also predisposes to CSVT (Tan et al. 2011).

### TREATMENT AND OUTCOMES IN CSVT

Two current paediatric stroke guidelines provide evidence-based recommendations for CSVT management (Roach et al. 2008; Paul Monagle et al. 2012). An additional European consensus guideline on paediatric CSVT treatment was also published in 2012 (Lebas et al. 2012). Finally, AHA guidelines for diagnosis and management of CSVT including children are also available (Saposnik et al. 2011): evidence across these sources is modest, resting predominantly on uncontrolled but clinically relevant paediatric and adult studies. First principles of acute care and neuroprotection described above remain a priority.

Promotion of endogenous thrombolytic mechanisms with anticoagulation to prevent thrombus progression and promote recanalisation is the primary medical intervention in CSVT. Best available evidence comes from a large single-centre study of 162 infants and children with CSVT treated by anticoagulation protocol (Moharir et al. 2010). Of 79 children, 56 (71%) received anticoagulation with significant haemorrhage reported in 5% and was not associated with worse outcome. Perhaps most importantly, propagation of thrombus within the first week occurred in nearly 30% of children who were not anticoagulated when using serial imaging compared to 5% who were: such propagation was associated with new infarction and worse outcome. Additional support for anticoagulation in childhood CSVT is provided by multiple adult clinical trials and cohort studies, smaller paediatric studies and paediatric trials in extra-cranial venous thrombosis. Multiple adult CSVT trials have provided evidence supporting improved survival and outcome with anticoagulation while meta-analysis confirms favourable safety and probable efficacy in reducing death and disability (Stam et al. 2003). Large cohort studies have confirmed the safety of anticoagulation in adult and paediatric CSVT (deVeber et al. 1998; Dix et al. 2000; deVeber et al. 2001; Sebire et al. 2005; Mallick et al. 2009).

The current consensus guidelines (Roach et al. 2008; Saposnik et al. 2011; Lebas et al. 2012; Paul Monagle et al. 2012) are in general agreement with each other regarding the indications, contraindications and duration of anticoagulation therapy. ‘Major’ cerebral or systemic haemorrhaging is a consistently stated relative contraindication to anticoagulation. If acute anticoagulation is not started repeat imaging within 5–7 days is suggested given risks of propagation (Moharir et al. 2010) while initial anticoagulation options include LMWH and UFH with relative risks and benefits as outlined above: paediatric dosing guidelines for each are available (Monagle et al. 2012). Anticoagulation duration parallels adult recommendations, usually given for 3 months (or 6 weeks in
neonates) followed by reimaging, with an additional 3 months (or 6 weeks in neonates) given if full recanalisation has not been achieved. If risk factors have been minimised or removed therapy is typically stopped at 6 months (3 months for neonates) regardless of the completeness of recanalisation. Despite this evidence practice patterns across paediatric stroke experts appear to vary widely (Jordan et al. 2010).

Additional therapeutic considerations for childhood CSVT include the following. Emergent recanalisation interventions are described for adult CSVT, however, must be considered experimental in children: limited adult evidence suggests possible efficacy of endovascular thrombolysis but a high rate of poor outcomes (Stamm et al. 2008). Paediatric experience consists of isolated patients (Prasad et al. 2006; Wasay et al. 2008): one single-centre case-series of 21 children with CSVT described thrombolytic therapy in four patients who had experienced severe thrombus progression despite initial anticoagulation (Mallick et al. 2009), with regional thrombolytics and guide wire manipulation accomplished without major complications. Decompressive hemicraniectomy has been performed with good outcome in isolated patients (Coutinho et al. 2009): increased intracranial pressure must be detected and monitored closely for attendant optic nerve damage and visual loss. At-risk children may require regular ophthalmological examinations, serial visual field testing and imaging and though evidence is lacking treatment options include carbonic anhydrase inhibitors, serial lumbar punctures, lumbo-peritoneal shunting or optic nerve sheath fenestration. Infection-related CSVT requires aggressive antibiotic therapy and, in some patients, surgical intervention (e.g. mastoidectomy). Corticosteroids are possibly harmful in adult CSVT and not recommended unless targeting a specific systemic inflammatory diseases: additional modifiable risk factors include hydration, restoration of iron stores, removal of jugular venous lines and modifying chemotherapy regimens.

Multiple cohort studies have defined outcomes after paediatric CSVT although few have used standardised outcome measures. Most lack long-term follow-up and shorter observation periods for young children may underestimate long-term developmental consequences. Consistent with this, 25% of children in the Canadian Paediatric Ischaemic Stroke Registry-Toronto outcome study showed increased severity of deficits over time (deVeber et al. 2001). Long-term, comprehensive neuropsychological studies are yet to be completed: children with CSVT require the same family-centred approach to rehabilitation, education and support as outlined above.

Rates of favourable outcome range widely from 26% to 75%, demonstrating a generally worse outcome than adult CSVT (Wasay et al. 2008) and mortality rates of 4–25% have been reported though primary causes of death is often not described. The largest population-based childhood CSVT study with mean follow-up 1.6 years reported 35% with deficits, 20% with epilepsy and 9% mortality (5% attributable to CSVT) (deVeber et al. 2001). A prospective single-centre study of 162 infants and children found no mortality in children older than 1 month but unfavourable outcome in 47% with 63% considered mild or normal (Moharir et al. 2010): intracranial hypertension, hydrocephalus and visual complications occur in up to 30% (Sebire et al. 2005; Mallick et al. 2009). Across adult and paediatric studies factors associated with poor outcome include coma at presentation, intracranial haemorrhage, bilateral infarction and deep system involvement (deVeber et al. 2001; Wasay et al. 2008): recurrence is uncommon but does occur, particularly in children with chronic risk factors. The largest study reported recurrence of cerebral or systemic thrombosis in 13% of children with CSVT (deVeber et al. 2001), a rate comparable to adults: ongoing risk factors must therefore be screened for and managed when possible. Incomplete recanalisation is common in children (Sebire et al. 2005; Vieira et al. 2009) but any influence on outcome is not well understood (Moharir et al. 2010).

**HAEMORRHAGIC STROKE**

Haemorrhagic stroke is a cerebrovascular event characterised by rupture of cerebral blood vessels often associated with neurological injury. Extravasation of blood occurs into intracranial compartments, the names of which are used for haemorrhagic stroke classification. Intracerebral (i.e. intraparenchymal) haemorrhage (ICH) is most common (50–75% of patients) and carries the greatest morbidity (Giroud et al. 1995; Lanthier et al. 2000). Subarachnoid haemorrhage (SAH) accounts for <25% of paediatric patients with aneurysms being most common. Intraventricular haemorrhage (IVH) usually represents an extension of ICH (Kumar et al. 2009): location influences differential diagnosis but haemorrhaging across multiple compartments is common. Haemorrhagic stroke is a neurological emergency with a high mortality rate, both acutely and later due to a high recurrence risk. Haemorrhagic stroke incidence is probably comparable to ischaemic stroke in children, estimated at one to five out of 100 000 children/year (Mallick and O’Callaghan 2009): compared to ischaemic stroke, there is increased need to find a specific aetiology, surgical treatment, mortality, chance of good outcome and recurrence in haemorrhagic stroke. (Fullerton et al. 2007a; Lo et al. 2008) Conditions predisposing to both ischaemic stroke and haemorrhagic stroke include moyamoya, sickle-cell, infectious and non-infectious vasculitis and certain congenital vasculopathies.

A number of single centre, retrospective cohort studies and case series have contributed to our understanding of paediatric haemorrhagic stroke (Livingston and Brown 1986; Lin et al. 1999; Lanthier et al. 2000; Blom et al. 2003; Lo et al. 2008; Kumar et al. 2009): these are presented in Table 15.3. To date, published paediatric stroke consensus guidelines
Table 15.3  Summary of published childhood haemorrhagic stroke case series

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Presentation</th>
<th>Lesion</th>
<th>Aetiology</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>(Lo et al. 2008)</td>
<td>N=85</td>
<td>HA (44)</td>
<td>ICH (72)</td>
<td>AVM (13)</td>
<td>Mortality (34)</td>
</tr>
<tr>
<td>7 years</td>
<td>US centre</td>
<td>N/V (28)</td>
<td>SAH (12)</td>
<td>Aneurysm (2)</td>
<td>Good (54)</td>
</tr>
<tr>
<td>64% male</td>
<td>LOC (55)</td>
<td>LOC (55)</td>
<td>IVH (8)</td>
<td>Cavernoma (8)</td>
<td>Epilepsy (0)</td>
</tr>
<tr>
<td>Median 7.0 years</td>
<td>FND (28)</td>
<td>Infra (13)</td>
<td>Tumour (15)</td>
<td>Heme (18)</td>
<td>Hydro (2)</td>
</tr>
<tr>
<td>*Includes non-trauma</td>
<td>SZ (22)</td>
<td>SDH (16)</td>
<td>Infection (6)</td>
<td>MMD (2)</td>
<td>Recurrence (NR)</td>
</tr>
<tr>
<td>SDH (16%)</td>
<td>N/S (19)</td>
<td></td>
<td></td>
<td></td>
<td>Lost (14)</td>
</tr>
<tr>
<td>(Al Jarallah et al. 2000)</td>
<td>N=68</td>
<td>HA (46)</td>
<td>NR</td>
<td>AVM (34)</td>
<td>Mortality (9)</td>
</tr>
<tr>
<td>8.5 years</td>
<td>N/V (14)</td>
<td></td>
<td></td>
<td>Aneurysm (6)</td>
<td>Good (50)</td>
</tr>
<tr>
<td>2 US centres</td>
<td>LOC (7)</td>
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<td></td>
<td>Cavernoma (3)</td>
<td>Epilepsy (10)</td>
</tr>
<tr>
<td>63% male</td>
<td>FND (21)</td>
<td></td>
<td></td>
<td>Heme (32)</td>
<td>Hydro (4)</td>
</tr>
<tr>
<td>Mean 7.1 years</td>
<td>SZ (37)</td>
<td></td>
<td></td>
<td>Tumour (13)</td>
<td>Recurrence (NR)</td>
</tr>
<tr>
<td></td>
<td>N/S (19)</td>
<td></td>
<td></td>
<td>AIS/CSVT (9)</td>
<td>Lost (NR)</td>
</tr>
<tr>
<td>(Blom et al. 2003)</td>
<td>N=56</td>
<td>HA/NV (12)</td>
<td>ICH (73)</td>
<td>AVM (41)</td>
<td>Mortality (35)</td>
</tr>
<tr>
<td>20 years</td>
<td>LOC (45)</td>
<td></td>
<td></td>
<td>Aneurysm (9)</td>
<td>Good (48)</td>
</tr>
<tr>
<td>Dutch centre</td>
<td>FND (38)</td>
<td></td>
<td></td>
<td>Heme (20)</td>
<td>Epilepsy (17)</td>
</tr>
<tr>
<td>48% male</td>
<td>SZ only (5)</td>
<td></td>
<td></td>
<td>Tumour (2)</td>
<td>Neuropysc (52)</td>
</tr>
<tr>
<td>Mean 7.7 years</td>
<td>N/S (NR)</td>
<td></td>
<td></td>
<td>Vasculitis (7)</td>
<td>Recurrence (21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic (20)</td>
<td>Lost (0)</td>
</tr>
<tr>
<td>(Kumar et al. 2009)</td>
<td>N=50</td>
<td>HA + N/V (70)</td>
<td>ICH (54)</td>
<td>AVM (44)</td>
<td>Mortality (6)</td>
</tr>
<tr>
<td>9 years</td>
<td>LOC (50)</td>
<td></td>
<td></td>
<td>Aneurysm (34)</td>
<td>Good (74)</td>
</tr>
<tr>
<td>Indian centre</td>
<td>FND (36)</td>
<td></td>
<td></td>
<td>Cavernoma (4)</td>
<td>Epilepsy (NR)</td>
</tr>
<tr>
<td>Mean 13.8 yrs</td>
<td>SZ (28)</td>
<td></td>
<td></td>
<td>MMD (6)</td>
<td>Recurrence (NR)</td>
</tr>
<tr>
<td>60% male</td>
<td>N/S (NR)</td>
<td></td>
<td></td>
<td>Heme (4)</td>
<td>Lost (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tumour (4)</td>
<td>Idiopathic (4)</td>
</tr>
<tr>
<td>(Lin et al. 1999)</td>
<td>N=42</td>
<td>HA (67)</td>
<td>ICH (100)</td>
<td>AVM (43)</td>
<td>Mortality (21)</td>
</tr>
<tr>
<td>9 years</td>
<td>N/V (50)</td>
<td></td>
<td></td>
<td>Aneurysm (0)</td>
<td>Good (70)</td>
</tr>
<tr>
<td>Taiwan centre</td>
<td>LOC (52)</td>
<td></td>
<td></td>
<td>Cavernoma (6)</td>
<td>Epilepsy (6)</td>
</tr>
<tr>
<td>Mean 10.3 years</td>
<td>SZ (38)</td>
<td></td>
<td></td>
<td>MMD (3)</td>
<td>Recurrence (6)</td>
</tr>
<tr>
<td>50% male</td>
<td>FND (19)</td>
<td></td>
<td></td>
<td>Heme (6)</td>
<td>Lost (NR)</td>
</tr>
<tr>
<td>No1 SAH</td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic (NR)</td>
<td></td>
</tr>
<tr>
<td>(Meyer-Heim and Boltshauser 2003)</td>
<td>N=34</td>
<td>HA (61)</td>
<td>ICH (88)</td>
<td>AVM (47)</td>
<td>Mortality (26)</td>
</tr>
<tr>
<td>10 years</td>
<td>N/V (45)</td>
<td></td>
<td></td>
<td>Aneurysm (15)</td>
<td>Good (53)</td>
</tr>
<tr>
<td>Swiss centre</td>
<td>LOC (42)</td>
<td></td>
<td></td>
<td>Cavernoma (12)</td>
<td>Severe (22)</td>
</tr>
<tr>
<td>Mean 7.1 years</td>
<td>FND (13)</td>
<td></td>
<td></td>
<td>Heme (12)</td>
<td>Rehab (40)</td>
</tr>
<tr>
<td>56% male</td>
<td>SZ (26)</td>
<td></td>
<td></td>
<td>DAVF (6)</td>
<td>Recurrence (9)</td>
</tr>
<tr>
<td></td>
<td>N/S (26)</td>
<td></td>
<td></td>
<td>Tumour (3)</td>
<td>Lost (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HTN (9)</td>
<td>Idiopathic (0)</td>
</tr>
<tr>
<td>(Livingston and Brown 1986)</td>
<td>N=27</td>
<td>HA (70)</td>
<td>ICH (100)</td>
<td>AVM (37)</td>
<td>Mortality (54)</td>
</tr>
<tr>
<td>10 years</td>
<td>N/V (74)</td>
<td></td>
<td></td>
<td>Aneurysm (11)</td>
<td>Good (NR)</td>
</tr>
<tr>
<td>UK centre</td>
<td>LOC (93)</td>
<td></td>
<td></td>
<td>Cavernoma (0)</td>
<td>Poor (NR)</td>
</tr>
<tr>
<td>Mean age NR</td>
<td>FND (63)</td>
<td></td>
<td></td>
<td>Heme (19)</td>
<td>Recurrence (NR)</td>
</tr>
<tr>
<td>59% male</td>
<td>SZ (33)</td>
<td></td>
<td></td>
<td>Tumour (15)</td>
<td>Lost (4)</td>
</tr>
<tr>
<td>No1 SAH</td>
<td></td>
<td></td>
<td></td>
<td>HTN (4)</td>
<td>Idiopathic (4)</td>
</tr>
<tr>
<td>(de Ribaupierre et al. 2008)</td>
<td>N=22</td>
<td>HA (77)</td>
<td>ICH (100)</td>
<td>AVM (55)</td>
<td>Mortality (9)</td>
</tr>
<tr>
<td>10 years</td>
<td>N/V (39)</td>
<td></td>
<td></td>
<td>Aneurysm (18)</td>
<td>Good (75)</td>
</tr>
<tr>
<td>2 Swiss centres</td>
<td>LOC (35)</td>
<td></td>
<td></td>
<td>Cavernoma (14)</td>
<td>Epilepsy (5)</td>
</tr>
<tr>
<td>Mean 10.8 years</td>
<td>FND (48)</td>
<td></td>
<td></td>
<td>Heme (0)</td>
<td>Recurrence (10)</td>
</tr>
<tr>
<td>41% male</td>
<td>SZ (14)</td>
<td></td>
<td></td>
<td>Idiopathic (9)</td>
<td>Lost (5)</td>
</tr>
<tr>
<td><strong>Heme excluded</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
focus on ischaemic stroke and do not address haemorrhagic stroke (deVeber and Kirkham 2008), with adult guidelines for haemorrhagic stroke management available and cited below where appropriate (Morgenstern et al. 2010). This section provides a general summary of clinical presentations, diagnostic imaging, treatment and outcomes followed by discussion of select childhood haemorrhagic stroke aetiologies. Related topics addressed elsewhere include preterm and perinatal haemorrhagic stroke (Chapter 1) as well as extra-axial subdural and epidural hematomas (Chapter 13).

### Clinical Presentations of Haemorrhagic Stroke

Sudden, severe, ‘thunderclap’ headache, particularly accompanied by neurological symptoms, is haemorrhagic stroke until proven otherwise. Headache with nausea and vomiting is the leading presenting symptom in children, reported in >50%, however, in one large series, although headache was reported in nearly 80%, only 30% had ‘sudden’ in onset (de Ribaupierre et al. 2008). Acute presentations are more typical of SAH and aneurysms than arteriovenous malformation (AVM) where symptoms can be subacute or chronic (Meyer-Heim and Boltschauser 2003). Warning or ‘sentinel’ bleed symptoms may resolve quickly but require careful attention and evaluation especially if associated with altered level of consciousness and focal neurological deficits. Seizures occur at presentation in 15–37% (Livingston and Brown 1986; Meyer-Heim and Boltschauser 2003; Lo et al. 2008; de Ribaupierre et al. 2008; Kumar et al. 2009), often leading to other diagnostic considerations and delaying haemorrhagic stroke diagnosis. Subtle and slowly progressive clinical presentations of haemorrhagic stroke in children are described in nearly half of patients (Livingston and Brown 1986; Meyer-Heim and Boltschauser 2003) while bulbar signs, ataxia and rapid-onset coma are typical of posterior fossa bleeds. Hypertension is common at presentation but may be a reactive, physiological response (Lo et al. 2008).

Similar to AIS, diagnostic delays are common in childhood haemorrhagic stroke, possibly related to lower index of suspicion in primary care physicians and less specific signs and symptoms, particularly in young children (Meyer-Heim and Boltschauser 2003; Lo et al. 2008; de Ribaupierre et al. 2008): following immediate stabilisation, thorough examination may suggest the underlying cause. Cranial bruits, skin lesions such as telangiectasias or purpura, infective endocarditis signs or genetic syndromes may be clues, while fever and meningismus may occur with subarachnoid blood but infection requires exclusion. A recently developed Paediatric ICH imaging score using variables of haemorrhage volume, hydrocephalus, herniation and posterior fossa location demonstrated clinically useful prognostic utility (Beslow et al. 2014). All children with suspected haemorrhagic stroke require continual vital signs monitoring, intensive nursing, frequent re-assessment and urgent neuroimaging.
Part VI  Tumours and Vascular Disorders

Figure 15.7  Aneurysm. A healthy 13-year-old girl presented with thunderclap headache and loss of consciousness. (a) Head CT demonstrated large intraparenchymal haemorrhage with intraventricular extension, effaced sulci and cisterns as well as enlarged temporal horns. (b) CT angiography demonstrated a large, complex aneurysm of the left middle cerebral artery with (c) conventional angiogram confirming same (left) with complete resolution following surgical repair (right). The child was well 2 years later with very mild hemiparesis and mild psychological morbidity.

Figure 15.8  Sickle cell moyamoya haemorrhage. (a, left) A 14-year-old girl with large vessel sickle-cell arteriopathy in a moyamoya pattern suffered bilateral watershed strokes as a young child. (a, right) After being stable for years on transfusions her last annual MRI demonstrated a small microbleed in the left basal ganglia on susceptibility-weighted imaging (arrow). (b) MRA showed otherwise stable severe arteriopathy with absent internal carotids. She developed a new headache that progressed over 2 hours to sudden vomiting and loss of consciousness, with (c) head CT demonstrating acute haemorrhage in the right thalamus with intraventricular extension and effaced cisterns. She required emergent intubation and extraventricular drain insertion; early recovery was good but she incurred multiple complications.

Diagnosis of Haemorrhagic Stroke

Neuroimaging

CT imaging should be completed without delay in children with suspected haemorrhagic stroke. The high risk of imminent mortality in haemorrhagic stroke would very seldom be outweighed by the very small lifetime risk of radiation in young children (Brenner and Hall 2007). Adult studies of SAH report CT sensitivities of 92–100% within 24–48 hours, 85% at 72 hours and 50% at 1 week (Edlow et al. 2008), while sensitivity and specificity of CT within 6 hours are 97–100% (Perry et al. 2011). In children given the lack of such evidence, adult data are extrapolated: acute blood is hyperdense on CT though at active haemorrhaging sites signal varies (see Figs 15.8 and 15.10). Immediate interpretation with attention to markers of mass effect and impending herniation is essential: quick volume estimation methods such as ABC/2 or ABC/XYZ provide prognostic information in children (Beslow et al. 2010; Kleinman et al. 2011). Acute CTA may be diagnostic of a root cause such as aneurysm or AVM (Fig. 15.7) while presence of a ‘spot sign’ or contrast extravasation on CTA also predicts early hematoma expansion in adults (Thompson et al. 2009). Serial CT may be required as early haematoma expansion may occur in >30% of childhood haemorrhagic stroke (Beslow et al. 2014).

Combined clinical and radiographic decision-making tools are in development to eliminate the need for lumbar puncture in some suspected haemorrhagic stroke patients with normal CT; however, these tools have not and will likely never be validated in children. Therefore, a child with clinically suspected haemorrhagic stroke and normal CT usually requires lumbar puncture to exclude xanthochromia. Time required for xanthochromia to develop in children is unknown but adult estimates of 6–8 hours appear reasonable (Edlow et al. 2008). Serial dilution of red cell counts across tubes is unreliable (Shah and Edlow 2002).
Occasional false negative conventional angiography may result from vasospasm, thrombosis or haemorrhage effects while another study of paediatric SAH suggests conventional angiography and MRA have comparable clinical utility (Fasulakis and Andronikou 2003). When a clear alternative aetiology has not been found children with haemorrhagic stroke should undergo conventional angiography to definitively exclude vascular pathology. Given the need for anesthesia combined diagnostic and interventional procedures may be indicated.

RISK FACTORS AND CAUSATION OF HAEMORRHAGIC STROKE

A cause can be defined for 85–90% of children with haemorrhagic stroke, with differential diagnoses outlined in Table 15.4.
Disorders of the blood vessels themselves as well as haematological factors must be considered. Inherent vascular disorders predominate (Livingston and Brown 1986; Lin et al. 1999; Lanthier et al. 2000; Blom et al. 2003; Meyer-Heim and Boltshauser 2003; Lo et al. 2008; de Ribaupeire et al. 2008; Kumar et al. 2009). The primary diseases of AVM, cavernoma and aneurysm are discussed in detail below including specific management: preceding that is an overview of additional aetiologies and review of general management principles and outcomes.

Numerous congenital arteriopathies leading to childhood haemorrhagic stroke are described. Hereditary haemorrhagic telangiectasia (HHT) (also known as Osler-Weber-Rendu) leads to systemic vascular malformations of the lung, liver and brain (Kring et al. 2005). Mutations in multiple transforming growth factor (TGF)-β signalling superfamily genes are dominantly inherited (Govani and Shovlin 2009). Management strategies including serial imaging and familial screening are available (Faughnan et al. 2011; McDonald et al. 2011) while inherited disorders of connective tissue such as COL4A1 predispose to recurrent haemorrhagic stroke (van der Knaap et al. 2006). Unique paediatric varieties of fibromuscular dysplasia predispose to childhood HA (Kirton et al. 2013) while a rapidly growing number of congenital cerebral vasculopathies have been associated with haemorrhagic stroke including MOPDII, PHACES and Alagille syndromes. Moyamoya (discussed above) carries increasing risk of haemorrhagic stroke with age that may be predictable by neuroimaging.

Acquired arteriopathies also cause haemorrhagic stroke in children. Infectious arteriopathies including mycotic aneurysms secondary to bacterial endocarditis and HIV vasculopathy may be particularly high risk for haemorrhagic stroke. Intracranial arterial dissection also carries a risk of paediatric SAH (Fullerton et al. 2001): other arteriopathies typically causing AIS but risking haemorrhagic stroke include sickle-cell vasculopathy, postradiation vasculopathy, post-traumatic vasculopathy as well as primary and secondary CNS vasculitides. Hypertension has been associated with 5–10% of childhood haemorrhagic stroke but recent studies suggest it is rarely a primary causative factor (Lo et al. 2008). Traumatic haemorrhagic stroke can occur in any compartment although most commonly are epidural or subdural and may appear as haemorrhagic contusions or smaller foci. Recent minor trauma may be associated with aneurysmal haemorrhage in children (Singhal et al. 2013) while unexplained haemorrhagic stroke in young infants should raise consideration of non-accidental trauma. One shaken baby syndrome study found subdural bleeds predominated (94%) but SAH (16%) and ICH (8%) also occurred (Morad et al. 2002). Haemorrhagic stroke can complicate dual arteriovenous fistulas (DAVF) which can be spontaneous or post-traumatic (Neumaier-Probst 2009): haemorrhaging into brain neoplasms accounts for 2–15% of patients (Lo et al. 2008) while iatrogenic haemorrhagic stroke may occur with neurosurgical procedures or intravascular interventions. CSVT infarcts often feature haemorrhagic transformation and can mimic primary haemorrhagic stroke (deVeber et al. 2001) while AIS transformation is also

Table 15.4 Disorders associated with haemorrhagic stroke in children

| Vascular – congenital |  |
|-----------------------|  |
| Arteriovenous malformations (AVM) |  |
| Hereditary haemorrhagic telangiectasia (HHT) |  |
| Cavernous malformations |  |
| Venous angiomas |  |
| Aneurysms |  |
| Primary/idiopathic |  |
| Fibromuscular dysplasias (FMD) |  |
| Loes–Dietz syndrome |  |
| Autosomal dominant polycystic kidney disease (ADPKD) |  |
| Majewski osteodysplastic primordial dwarfism (MOPDII) |  |
| Craniofacial arteriovenous metamic syndrome (CAMS)/Wyburn-Mason |  |
| Coarctation with intracranial aneurysm |  |
| Other |  |
| PHACES syndrome |  |
| COL4A1 mutations |  |
| Alagille cerebral vasculopathy |  |
| Sturge-Weber syndrome |  |
| Vascular – acquired |  |
| Arteriopathies |  |
| Arterial dissection (intracranial) |  |
| Moyamoya disease |  |
| Moyamoya syndrome (neurofibromatosis-1, trisomy 21) |  |
| Sickle cell disease |  |
| Vasculitis: childhood primary angiitis of CNS (cPACNS), secondary systemic vasculitis |  |
| Post-radiation vasculopathy |  |
| Cerebral proliferative angiopathy (CPA) |  |
| Bacterial endocarditis (mycotic aneurysm) |  |
| Infection: bacterial meningitis, cerebritis, or abscess; herpes encephalitis |  |
| HIV vasculopathy |  |
| Cerebral neoplasms |  |
| Trauma, non-accidental trauma |  |
| Dural arteriovenous fistulas (DAVF) |  |
| Haemorrhagic transformation of ischaemic stroke (CSVT > AIS) |  |
| Non-vascular |  |
| Coagulopathy |  |
| Hemophilia or other factor deficiencies (Vitamin K, VIII, XIII) |  |
| Disseminated intravascular coagulation (DIC) |  |
| Haematological malignancy and/or treatments including BM transplant |  |
| Hepatic failure |  |
| Thrombocytopenia |  |
| Immune thrombotic purpura (ITP) |  |
| Hemolytic uraemic syndrome (HUS) – acquired and congenital |  |
| Thrombotic thrombotic purpura (TTP) |  |
| Medications |  |
| Thrombolytics, antiocoagulants, antiplatelet agents, cocaine, amphetamines, sympathomimetics |  |
| Hypertension |  |
| Iatrogenic |  |
| Cerebral angiography, angioplasty/stenting, neurosurgery |  |

Part VI Tumours and Vascular Disorders
common (Beslow et al. 2011; Schechter et al. 2012) and needs to be differentiated from primary haemorrhagic stroke.

Haemorrhagic diatheses as the primary cause for haemorrhagic stroke occurs more commonly in children than adults (Roach and Riela 1995). Such haematological factors occur in up to 30% of patients (Livingston and Brown 1986; Lanthier et al. 2000; Blom et al. 2003; Meyer-Heim and Bolshhauser 2003; Kumar et al. 2009) with one study reporting 32% including thrombocytopenia, coagulation factor deficiencies or sickle-cell disease (Fig. 15.8) (Al Jarallah et al. 2000). Other haemorrhagic diatheses include genetic factor deficiencies such as hemophilia, haematological malignancies and their treatment, as well as hepatic failure. Thrombocytopenia can be secondary to infectious, immune or oncological disease and screening for medication, accidental ingestion and illicit drug use should include consideration of intoxication with anticoagulants, antiplatelet agents, sympathomimetic drugs, cocaine and amphetamine (Forman et al. 1989; Levine et al. 1990). Children with haemorrhagic stroke require immediate laboratory hemostatic evaluations including complete blood count, prothrombin and partial hromboplastin times, as well as international normalised ratio.

**TREATMENT IN HAEMORRHAGIC STROKE**

The fundamental principles of acute brain injury management outlined above apply to the child with haemorrhagic stroke. Immediate consultation of a paediatric neurosurgeon is essential as neurosurgical intervention is required in 60–80% of patients (Livingston and Brown 1986; Blom et al. 2003; Meyer-Heim and Bolshhauser 2003; de Ribauipierre et al. 2008; Kumar et al. 2009): procedures include hematoma evacuations though clear evidence-based indications or even accurate predictive tools do not exist for children. Placement of intraventricular drains and intracranial pressure monitoring devices is often indicated to maintain cerebral perfusion while additional surgical procedures may include removal or embolisation of AVMs, clipping or coiling of aneurysms, tumour removal and VP shunts for posthaemorrhagic hydrocephalus.

Medical management of childhood HA focuses on supportive neuroprotective care as outlined above. Acute seizures are common and may exacerbate intracranial hypertension or occur subclinically, suggesting a role for EEG monitoring (Beslow et al. 2013). Treatment or underlying conditions includes antibiotics for endocarditis, replacement of deficient factors (e.g. factor VIII in hemophilia), reversal of antithrombotic medications (e.g. vitamin K, protamine, platelet transfusion) and immunomodulatory therapy for inflammatory conditions (e.g. ITP). Recombinant factor VIIa (rFVIIa) within 4 hours appeared to improve haemorrhage and neurological outcomes in adults but carried high thrombotic complications, while applications in children are not defined.

**OUTCOMES IN HAEMORRHAGIC STROKE**

When compared to childhood ischaemic stroke long-term outcomes are better for haemorrhagic stroke but early mortality is higher (Lo et al. 2013): a summary of the outcomes from the largest studies to date is found in Table 15.2. Across all studies mortality rates ranged from 6–54% and epilepsy in 0–17% to overall ‘good’ outcome in 50–75%. A long-term outcome study of 56 children including detailed neuropsychological testing reported 65% survival with 50% having favourable outcomes (Blom et al. 2003) while hemiparesis persisted in 31% though typically not severe, with 17% having epilepsy. Additional adverse outcomes include visual deficits, language disorders and ataxia after posterior fossa haemorrhagic stroke, with hydrocephalus requiring shunting after intraventricular haemorrhage. Nearly half of children will require some formal rehabilitation (Meyer-Heim and Bolshhauser 2003): a paediatric imaging ICH score of 2 or more based on larger bleed size predicts severe outcome or death with sensitivity and specificity of 90% and 68% (Beslow et al. 2010; Lo et al. 2013; Beslow et al. 2014). Other accurate outcome predictors for childhood haemorrhagic stroke remain to be determined, with factors associated with poor outcome including delayed diagnosis, impaired consciousness at presentation, posterior fossa location (Higgins et al. 1991; Kumar et al. 2009) as well as aetiology and associated diagnoses (Lo et al. 2013). Mortality appears highest with acute posterior fossa bleeds (Livingston and Brown 1986) while risk of epilepsy may be associated with need for acute intervention (Beslow et al. 2013).

Recurrence of paediatric haemorrhagic stroke is common, requiring treatment of at risk lesions and careful long-term surveillance. One population-based study suggested 5-year cumulative recurrence rates of 10%, most within 6 months (Fullerton et al. 2007a) while another longer-term study found recurrence in 21% over 10 years (Blom et al. 2003). AVM recurrence rates are comparable to adults, ~2% per year (Fullerton et al. 2005), however, in contrast to many adults paediatric decisions must consider a risk duration lasting many decades for persistent lesions. Additional risk reduction strategies such as activity restriction and avoidance of contact sports are not well studied.

**SPECIFIC VASCULAR DISEASES CAUSING CHILDHOOD HAEMORRHAGIC STROKE**

**ARTERIOVENOUS MALFORMATIONS**

Vascular malformations are developmental anomalies with preserved connections between normal vessels. Malformations can be divided into four histological types: arteriovenous malformations (AVMs), cavernous malformations, venous angiomas and capillary telangiectasias, with the last two not causing haemorrhagic stroke, with cavernomas discussed below. True
CAVERNOUS MALFORMATIONS

Cavernous malformations are dense collections of thin, dilated, vascular channels without intervening brain parenchyma which change over time, accruing microbleeds, thrombosis and calcification. Studies of childhood cavernous malformations are limited (Acciarri et al. 2009; Bhardwaj et al. 2009) though recent large case series appear to support previous reports (Gross et al. 2013), while pathogenesis is increasingly understood through the elucidation of multiple genetic causes. Dominantly inherited familial cavernous malformations syndromes typically include multiple cerebral and retinal lesions with an accompanying higher risk of haemorrhaging (Sirvente et al. 2009): children treated with cranial irradiation are also at increased risk.

Clinical presentations in children are approximately evenly distributed between seizures, focal deficits or symptomatic haemorrhage (Lee et al. 2008). On average, paediatric cavernous malformations are larger, bleed more and have associated vascular anomalies compared to adults. Annualised risk of haemorrhaging with cavernous malformations is less than AVM and aneurysm, estimated at <0.25% annually (Del Curling et al. 1991) while bleed size is also typically small, with life-threatening haemorrhage being rare. The exception are brainstem cavernous malformations where pontine locations predominate and higher morbidities from haemorrhaging may influence management (Bhardwaj et al. 2009). Modern MRI with highly sensitive sequences for detecting microbleeds has increased cavernous malformations diagnosis (see Fig. 15.10): lesions are usually well demarcated, spherical, heterogeneous ‘popcorn’ lesion with mixed T1 and T2 intensities and evidence of blood (Mottolese et al. 2001). Angiography is usually normal aside from associated vascular malformations.

Unruptured lesions in non-eloquent locations may be managed expectantly, with surgical resection usually indicated for children with epilepsy, deficits or critically located lesions (Roach Riela 1995; Punt 2004) but the role of radiosurgery appearing limited (Mottolese et al. 2001). In a recent large series of 181 children with lobar cavernous malformations surgery in 83 was associated with older age and larger symptomatic lesions (Gross et al. 2013) with none of the 98% completed resected patients having recurrence over nearly 5 years and complication rate of 5%. Another series of 42 children undergoing cavernous malformations surgical resection reported 69% with favourable outcome and low complication rates of 7% associated with critically located lesions (Acciarri et al. 2009). Cavernous malformations surgery for epilepsy is often curative (Consales et al. 2009; Gross et al. 2013) while brainstem cavernous malformations surgery in children is likely to be influenced by location, size, approximation to the pial surface, child age and history of radiation (Bhardwaj et al. 2009).

ANEURYSMS

Aneurysms are focal enlargements of arteries secondary to compromised wall integrity. All three arterial wall layers – intima, media, adventitia – are involved. Pseudoaneurysms are enlargements involving fewer than three layers. Less than 5% of brain aneurysms become symptomatic in childhood. Across the largest case-series of childhood haemorrhagic stroke, aneurysms represent 2–34% of patients (see Table 15.2). Population-based data suggests childhood SAH is usually due to aneurysms, representing >10% of paediatric haemorrhagic stroke (Jordan et al. 2009). Paediatric aneurysms usually present with SAH, often with extension into parenchyma, intraventricular and extra-axial spaces (Lasjaunias et al. 2005), with headache and encephalopathy the leading
clinical manifestations (Jordan et al. 2009). Large lesions may feature progressive focal deficits in children, whereas the inverse of adults (Ostergaard 1991). Children, particularly infants, are more likely to harbour giant aneurysms (>10cm), found in up to 50% of children with aneurysms (Kasahara et al. 1996). Posterior circulation location is more common in children, found in 20–27% (Khoo and Levy 1999): on average, infants typically have larger aneurysms of major intracranial vessels while older children have smaller lesions favouring the internal carotid bifurcation (Khoo and Levy 1999; Jordan et al. 2009).

Aneurysms in children are more heterogeneous than in adults. Saccular aneurysms are relatively common and may reflect congenital conditions causing arterial wall weakness and aneurysms with presentations early in life (Khoo and Levy 1999). Pathophysiology is not well understood but a growing list of both congenital and acquired vascular diseases are associated with childhood cerebral aneurysms (Table 15.4). Genetic aetiologies are increasingly defined through research initiatives like the Familial Intracranial Aneurysms Study (Broderick et al. 2009): examples include connective tissue disorders like COL4A1, Ehlers-Danlos syndrome and polycystic kidney disease, with many such inherited aneurysms appearing to carry higher risks of early and recurrent haemorrhage. Multiple aneurysms occur in Majewski osteodysplastic primordial dwarfism (MOPD-II) causing fatal SAH during childhood in most. Aneurysms and SAH occur in childhood forms of fibromuscular dysplasia (Kirton et al. 2013), while arterial dissections are a common cause of childhood pseudoaneurysms (Lasjaunias et al. 2005; Tan et al. 2009). Trauma-induced arterial injury may result in aneurysm formation while infectious cerebral emboli in bacterial endocarditis results in local arteritis, compromising wall integrity and leading to mycotic aneurysm formation over days to months that must be monitored (Brust et al. 1990). Other infectious arteriopathies, particularly HIV, may result in aneurysm formation in children.

CT/CTA can usually confirm both SAH and an aneurysmal source (Fig. 15.7) while MRI may add information including evidence of older bleeds and parenchymal injury. MRA has limited resolution for small lesions but non-invasive vascular imaging can diagnose complications such as vasospasm. Conventional angiography is the criterion standard to diagnose, characterise, and plan management of aneurysms with aneurysm characteristics used to guide treatment options including direct surgical clipping and interventional procedures. Coilings of aneurysms with insertion of metal particles resulting in thrombosis and obliteration is increasingly reported in children: a series of 23 children with heterogeneous aneurysms treated endovascularly reported a high angiographic cure rate and good medium term outcome in >95% (Saraf et al. 2012). A recent more than 20-year follow-up of over 100 children with aneurysms found surprisingly high excess long-term mortality attributable to aneurysms, suggesting long-term follow-up is essential (Koroknay-Pal et al. 2012).

VEIN OF GALEN MALFORMATIONS

Vein of Galen malformations (VGAM) form early in embryogenesis with abnormal feeding by choroidal arteries and do not connect to the deep venous system, with lesions most often presenting early in infancy with high-output heart failure secondary to intracranial shunting and cranial bruit. Macrocephaly occurs secondary to venous hypertension and hydrocephalus: brain injury often results from progressive, diffuse cerebral infarction, sometimes called the ‘melting brain’, the pathophysiology of which is incompletely understood. Antenatal ultrasound diagnosis in >30% is associated with worse outcome (Rodesch et al. 1994; Alvarez et al. 2007) with CT or MRI showing a large dilated vascular channel in the region of the Vein of Galen. MRI is most sensitive to parenchymal injury with MRA, while MRV characterises vascular anatomy: only conventional angiography can establish the number and origin of feeding arteries and venous drainage.

VGAM management is enormously challenging. A score combining neurological, cardiac and systemic involvement with lesion characteristics helps select children for emergent intervention, delayed surgery or palliative care (Alvarez et al. 2007; Geibprasert et al. 2010). Stable neonates are often followed for 4–6 months before intervening: those with refractory heart failure, hydrocephalus or neurological deterioration are treated earlier. Embolisation procedures typically involve injection of material into feeding arteries to reduce shunting and restore haemodynamic stability. A series of 317 VGAM children dominates the published experience (Lasjaunias et al. 2006; Alvarez et al. 2007). Case series from other leading institutions (Lasjaunias et al. 1996; Fullerton et al. 2003; Lasjaunias et al. 2006; Heuer et al. 2010; Li et al. 2011; Berenstein et al. 2012) total...
Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ (2009) Care of infants and children with stroke requires a team approach ideally in a centre with paediatric stroke expertise, paying attention to the children with stroke: guidelines of paediatric stroke. Many current approaches to the clinical care of infants and children with ischaemic stroke are based on logical extension from adult stroke and other forms of paediatric thrombosis. Each child should be approached with knowledge of the current guidelines and an individualised appreciation of the stroke syndrome of the child: guidelines will undoubtedly change as stronger levels of evidence become available in future studies. The optimal care of infants and children with stroke requires a team approach ideally in a centre with paediatric stroke expertise, paying attention to the child and family.

In summary, we are in an era of rapid discovery in the field of paediatric stroke. Many current approaches to the clinical care of infants and children with ischaemic stroke are based on logical extension from adult stroke and other forms of paediatric thrombosis. Each child should be approached with knowledge of the current guidelines and an individualised appreciation of the stroke syndrome of the child: guidelines will undoubtedly change as stronger levels of evidence become available in future studies. The optimal care of infants and children with stroke requires a team approach ideally in a centre with paediatric stroke expertise, paying attention to the child and family.

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*Alexis Arzimanoglou and Michael S Duchowny*

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Epilepsy and Other Seizure Disorders

Alexis Arzimanoglou and Michael S Duchowny

Epilepsy is neither a disease nor a syndrome, but rather a symptom with multiple causes, genetic or lesional, representing a very significant part of neurology that may present in a variety of conditions and circumstances. It is not possible to describe all manifestations in this chapter, and the reader is referred to publications by Arzimanoglou et al. (2004, 2016), Bureau et al. (2012), Engel and Pedley (2007) and Duchowny et al. (2013). Clinical epileptic seizures are the most characteristic but not sole manifestation of electrographic activation as interictal abnormalities are also an important part of its semiology. This applies to electroencephalogram (EEG) manifestations as well as to clinical disturbances, especially neurological, cognitive and behavioural ones that may be present interictally.

TERMINOLOGY AND DEFINITIONS

Epileptic seizures are transient clinical events that result from abnormal and excessive activity of synchronised, more or less extensive populations of cerebral neurons. This abnormal activity results in paroxysmal disorganisation of one or several brain functions, manifested by positive, excitatory phenomena (motor, sensory, psychic) or negative phenomena (such as loss of awareness, of muscle tone or of language), or by a mixture of the two. The clinical events that constitute epileptic seizures can be extremely diverse, and no single manifestation is essential. A detailed description of the ictal event is the cornerstone of accurate diagnosis.

The EEG events that underlie the seizure constitute the epileptic discharge, which in some cases may remain without clinical expression or have only subtle clinical consequences, referred to as ‘subclinical seizures’ (Gastaut 1973). The seizure discharge and/or clinical seizure may remain localised or be expressed bilaterally and synchronously over most of the cortical surface – the so-called generalised seizure. In this chapter, the term ‘seizure’ is used in its etymological sense (from ‘to seize’) and applied to both epileptic and nonepileptic events (Stephenson 1990), although it is more often reserved for seizures caused by an epileptic mechanism.

Epileptic seizures may result from intercurrent events such as fever, hypoglycaemia or acute central nervous system (CNS) infections (occasional seizures), or may recur spontaneously without a known precipitant (unprovoked epileptic seizures that, when repeated, constitute epilepsy). The dividing line between isolated (or occasionally provoked) and unprovoked epileptic seizures is not always evident. In fact, isolated (occasional) seizures can have a recognisable cause, or may be unprovoked. However, factors that either precipitate the attack or contribute to arresting it must exist. Many precipitating factors such as intermittent photic stimulation, certain sounds or lack of sleep, are well-recognised but many more are unknown, imperfectly described or only suspected. Stress, psychological factors and fatigue are likely to be responsible for precipitating a sizeable proportion of epileptic seizures, but their mechanisms of action are largely unexplored. The term ‘occasional seizure’ is ambiguous. It may imply that a paroxysmal epileptic event may only occur once under given circumstances (thus, by definition, not considered as epilepsy). However, ‘occasional’ may also mean that an event (in this case a seizure) can recur from time to time, under the same circumstances.

Some confusion is caused by the interchangeable use of the terms ‘provoked’ and ‘triggered’. Provoking factors include fever, head injury, excessive alcohol intake, withdrawal from alcohol or drugs, hypoglycaemia, electrolyte disturbance, brain infection, ischaemic stroke, intracranial haemorrhage and pro-convulsive drugs (Pohlmann-Eden et al. 2006). Seizures following psychological stress or sleep deprivation are not considered ‘acute symptomatic’ but rather ‘triggered’ by these factors in susceptible individuals. Reflex seizures are also considered to be triggered by a given stimulus (stroboscopic lights, reading, etc.). Most seizures are likely to be multifactorial in origin.

Epilepsy should be considered as a more enduring condition, or a group of conditions, in which epileptic seizures occur repeatedly without a detectable cause (Gastaut 1973) due to structural brain damage or an intrinsic functional propensity. For epidemiological purposes, the term epilepsy was defined as at least two seizures separated in time. In clinical practice, it refers to a lasting, ‘chronic’ condition and may be
more than the repetition of seizures (Aicardi 1997). Subclinical epileptic activity, especially if prolonged, is likely to disorganise many brain functions and causes transient or lasting cognitive and behavioural disturbances (Tassinari et al. 1992; Arzimanoglou et al. 2005).

In 2014, the International League Against Epilepsy (ILAE) accepted the recommendations of a task force altering the practical definition of epilepsy in special circumstances that do not meet the criteria of two unprovoked seizures (Fisher et al. 2014). The task force proposed that epilepsy be considered a brain disease defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
3. Sufficient elements present allowing the diagnosis of an epilepsy syndrome.

Convolusions are episodes of involuntary muscle contractions that are either sustained (tonic) or brief (clonic). In principle, convulsions may be either epileptic or nonepileptic in nature. However, the term is traditionally used to designate epileptic seizures, including occasional epileptic seizures such as febrile convulsions, because they are almost exclusively marked by motor phenomena, and because the term has come to convey the idea of benignity. Nevertheless, the clinician must still remember that most infantile convulsions, including febrile seizures, are indeed epileptic seizures.

MECHANISMS OF EPILEPTIC SEIZURES

The epileptic discharge, which is the basic electrophysiological feature of epileptic seizures, typically consists of rhythmical and high-amplitude oscillations of electrical potential that can usually be recorded on the scalp EEG but may, in some cases, remain undetectable even on the cortical surface, depending on their depth, the volume of brain involved, its geometry and the manner of propagation (Bancaud and Talairach 1975). It is direct evidence of the abnormal, excessive neuronal activity postulated by Hughlings Jackson as the origin of epilepsy. Both the scalp and cortical epileptic discharge are related to the abnormal excitability of individual neurons and the excessive synchronisation of a large cellular population. As shown schematically in Figure 16.1, EEG spikes correspond to the summation of field potentials that are themselves the direct consequence of intracellular events. The most remarkable of these, in seizures of focal origin, is an enormous increase in the size of membrane depolarisation induced by excitatory postsynaptic potentials and the paroxysmal depolarisation shift. This corresponds to a spike on the interictal EEG record, at a threshold level of affected neurons that is followed by a prolonged increased after-polarisation. This hyperpolarisation disappears during a seizure allowing repetitive bursting to go unchecked. This in turn recruits neighbouring neurons that discharge synchronously.

Different mechanisms may be operative in generalised seizures, but all convulsive seizures involve sustained membrane depolarisation. The mechanism of nonconvulsive seizures such as absences, on the other hand, involves a succession of excitatory and inhibitory potentials (Snead 1995). The EEG slow-wave discharge reflects gamma-aminobutyric acid (GABA)-mediated increased inhibition, which, together with enhanced excitation, leads to a state of epileptic hypersynchrony. Low-threshold calcium currents in reticular thalamic pacemaker neurons are likely to be responsible for the hypersynchronous spike–wave discharges of absence epilepsy. Gloor and Fariello (1988) postulated that primary generalised epilepsy is characterised by a diffusely hyper-excitatory cortex, so that an epileptic discharge can be triggered by excitation of the thalamic reticular system induced by the thalamocortical input, and thus both cortical and subcortical structures are necessary for its genesis.

Detailed studies of the mechanisms responsible for the generation of epileptic discharges is beyond the scope of this book (for reviews see Jones 2006; Hirsch et al. 2006a; Najm et al. 2006b).
The enhanced neural excitability observed in epilepsy may result from a genetically determined imbalance of excitatory and inhibitory neurotransmitters, from changes in cortical circuitry, or from the irritability of a localised lesion. In this regard, the possible influence of abnormally discharging neurons on the rest of the brain has attracted considerable attention. Focal subclinical stimulation of neuronal groups becomes increasingly effective with properly repeated stimulations and eventually may result in generalised seizures (Moshé and Ludvig 1988). The relevance of this ‘kindling’ phenomenon for human epilepsy, however, is still undetermined, although it may be a factor in the emergence of secondary foci (Morrell 1989).

Decreased inhibitory mechanisms are thought to play an important role in epilepsy, and the main cortical inhibitory neurotransmitter, GABA, has been studied extensively. The GABA hypothesis has been at the origin of major therapeutic efforts and of the development of important antiepileptic drugs.

Current research is also directed toward excitatory neurotransmitters such as glutamate and aspartate, an excess of which could account for the local or generalised enhanced cortical excitability (Najm et al. 2006b). Changes in the receptors of both excitatory (glutamate and aspartate) and inhibitory (GABA) neurotransmitters probably modulate cortical excitability, and their differential rates of maturation may explain the changing susceptibility to epilepsy at various ages (Moshé 1987; Johnston 1996; Holmes 1997).

Whatever the mechanisms involved, brain maturation plays a critical role in the susceptibility to seizures and in their clinical expression. The morphological, electrophysiological and biochemical bases of brain maturation in relation to seizures are being actively explored (Jensen 1999; Ben-Ari 2006; Dulac et al. 2013).

AETIOLOGY OF THE EPILEPSIES

Occasional epileptic seizures, which are almost always generalised, can be provoked by a host of intercurrent events (Table 16.1) including fever, hypoglycaemia, metabolic imbalance or acute diseases (Fig. 16.2).

Provoking factors can result from acute conditions, such as structural brain damage from trauma, metabolic disturbances or infections which occur in children without any predisposition to seizures. More commonly, however, a special predisposition to seizures, that is likely to be genetic in origin and often age-dependent, renders the individual susceptible to specific stimuli, of which the most common example is febrile seizures. However, both factors may operate concurrently. For example, structural lesions precipitate seizures more frequently in patients with a family history of epilepsy than in the general population, and the same may apply to other causes, for example, acute meningitis.

Epilepsy (as a chronic disorder) can also be due exclusively to genetic factors or chronic brain damage (congenital or acquired), or to various combinations (Berkovic et al. 1987; Hani et al. 2015).

The epilepsies are usually divided into idiopathic, symptomatic and cryptogenic cases. Idiopathic epilepsies are those with no detectable brain lesion or abnormality; symptomatic epilepsies result from brain abnormalities or acquired damage; cryptogenic epilepsies have no demonstrable organic cause. The frequency of this last category has decreased as refinements to the methods of investigation are made. The ILAE Commission on Classification and Terminology published, in 2017, a proposal for a revised terminology ‘genetic, structural–metabolic, and unknown representing modified concepts to replace idiopathic, symptomatic and cryptogenic’ (Scheffer et al. 2017). The pros and cons modifications and evolution of the terminologies used are discussed below.

Figure 16.2 Generalised epileptic seizure in 2-month-old infant with hypernatraemia. Tonic discharge (top left), followed by clonic discharge (top right, continued bottom left). Trace (at bottom right) was recorded at slow paper speed and shows termination of seizure.

The EEG features of this seizure are slightly atypical, for example, the rhythm of the tonic discharge is not the same over both hemispheres. This is common in infants, in whom typical generalised seizures are rare.

Genetic factors are of paramount importance in the epilepsies unassociated with neurological abnormalities (idiopathic epilepsies) but may also influence epilepsies associated with demonstrable brain damage (Ottman 1989, 2005), focal cortical dysplasias being a recent example (Leventer et al. 2014).

The role and mode of inheritance vary with the type of epilepsy, and known genetic data will be indicated for each epilepsy syndrome (Table 16.2a summarises identified genes for epilepsy per gene and Table 16.2b identified genes per
### Table 16.1 Main causes of occasional epileptic seizures

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever due to extracranial infections</strong> (febrile convulsions)</td>
<td></td>
</tr>
<tr>
<td><strong>Intracranial infections</strong></td>
<td>Meningitis, brain abscess, empyema</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td>Meningitis, brain abscess, empyema</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td>Viral meningitis, encephalitis</td>
</tr>
<tr>
<td><strong>Fungal or parasitic</strong></td>
<td>Brain infections</td>
</tr>
<tr>
<td><strong>Parainfectious encephalopathies</strong></td>
<td>Reye syndrome</td>
</tr>
<tr>
<td><strong>Other acute encephalopathies of obscure origin</strong></td>
<td>Other acute encephalopathies of obscure origin</td>
</tr>
<tr>
<td><strong>Haemorrhagic shock</strong></td>
<td>Haemorrhagic shock</td>
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<tr>
<td><strong>Metabolic disturbances</strong></td>
<td>Hypocalcaemia and hypomagnesaemia</td>
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<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>Hypoglycaemia</td>
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<tr>
<td><strong>Hyponatraemia</strong></td>
<td>Inappropriate secretion of antidiuretic hormone</td>
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<tr>
<td></td>
<td>Water intoxication</td>
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<tr>
<td></td>
<td>Inadequate rehydration</td>
</tr>
<tr>
<td><strong>Hyponatraemia</strong></td>
<td>Consequence of vascular collapse due to dehydration</td>
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<tr>
<td></td>
<td>Consequence of rapid correction of sodium levels</td>
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<tr>
<td><strong>Inborn errors of metabolism (especially during episodes of decompensation)</strong></td>
<td>Inborn errors of metabolism (especially during episodes of decompensation)</td>
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<tr>
<td><strong>Intoxications</strong></td>
<td>Endogenous</td>
</tr>
<tr>
<td><strong>Uraemia, renal dialysis</strong></td>
<td>Renal disease</td>
</tr>
<tr>
<td><strong>Hepatic encephalopathy</strong></td>
<td>Diabetic ketoacidosis</td>
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<tr>
<td><strong>Hypertensive encephalopathy</strong></td>
<td></td>
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<tr>
<td><strong>Renal disease</strong></td>
<td>Acute nephritis (may be paucisymptomatic)</td>
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<tr>
<td><strong>Haemolytic–uraemic syndrome</strong></td>
<td>Haemolytic–uraemic syndrome</td>
</tr>
<tr>
<td><strong>Head trauma</strong></td>
<td>Early epileptic seizures</td>
</tr>
<tr>
<td><strong>Extradural/subdural haematoma</strong></td>
<td>Brain contusion</td>
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<tr>
<td><strong>Acute cerebral hypoxia</strong></td>
<td>Cardiac arrest</td>
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<tr>
<td><strong>Drowning</strong></td>
<td>Acute vascular collapse</td>
</tr>
<tr>
<td><strong>Cerebrovascular accidents</strong></td>
<td>Arterial occlusion (thrombosis or embolism)</td>
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<tr>
<td><strong>Venous thrombosis</strong></td>
<td>Venous thrombosis</td>
</tr>
<tr>
<td><strong>Haemorrhage from vascular malformations</strong></td>
<td>Haemorrhage from vascular malformations</td>
</tr>
<tr>
<td><strong>Burns encephalopathy</strong></td>
<td>Burns encephalopathy</td>
</tr>
</tbody>
</table>

Table 16.1 Main causes of occasional epileptic seizures

Epilepsy syndrome. Mono-factorial origin has been demonstrated in some genetic syndromes, and rapid progress is being made in the molecular genetic basis of childhood epilepsy (for reviews and evolution of concepts see Battaglia and Guerrini 2005; Duron et al. 2005; Gardiner 2005; Heron et al. 2007; Hani et al. 2015). Only a small proportion of cases (1–2%) demonstrate single-locus traits such as tuberous sclerosis or metabolic errors. Epilepsy syndromes with a monogenic dominant transmission, described below, include benign neonatal convulsions (Leppert et al. 1989), benign infantile seizures (Vigezano et al. 1992; Echenne et al. 1994), and familial frontal (Scheffer et al. 1995a), familial mesial temporal lobe and familial lateral temporal lobe (Berkovic et al. 1996; Andermann and Kobayashi 2005) epilepsy syndromes.

The role of genetic factors is not limited to these relatively rare cases. A number of genes are operative in the genesis of multigenic epilepsy. Complex inheritance is much more common (Turnbull et al. 2005) even though dominant inheritance has been suggested for epilepsies with 3Hz spike–wave activity and possibly some forms of photosensitive epilepsy (Doose and Waltz 1993). Doose and Baier (1987) suggested that certain EEG traits (e.g. photosensitivity or spontaneous spike–wave paroxysms) could be inherited independently and that the combination of such EEG traits (and probably other factors) might account for the inherited propensity to various forms of epilepsy. Complex inheritance (multifactorial inheritance) even accounts for some syndromes once thought to be dominant, for example, in juvenile myoclonic epilepsy, for which a dominant gene had been identified (Greenberg et al. 1988), several other genes now appear to be implicated.

The current view is that many epilepsy genes are susceptibility rather than unconditional genes, whose conjugated action and additional environmental factors augment the probability of clinical epilepsy, thus accounting for the observation that siblings or parents of affected persons may be normal or present with a different epilepsy syndrome. A detailed presentation of current knowledge on the genetics of the epilepsies is beyond the scope of this book (for reviews see Pandolfo 2013; Hani et al. 2015; McTague et al. 2016; ILAE Consortium on Complex Epilepsies 2016; Striano and Zara 2017; and refer to specific sections per syndrome for more focussed references).

Brain injury is a major aetiologic factor in focal or generalised epilepsies associated with clinical evidence of neuro-developmental defects. Selected causes include cortical malformations, tuberous sclerosis complex or Sturge–Weber syndrome-related lesions, brain tumours, trauma, hippocampal sclerosis and vascular abnormalities. The main aetiologic factors of brain injury associated with epilepsy are shown in Table 16.3.

The term symptomatic (or ‘structural’, see Berg et al. 2010; Scheffer et al. 2016) is used for lesions that produce clinical or gross radiological signs, cognitive impairment and/or definite neuroimaging abnormalities. Microscopic lesions, not detectable during life, also play a considerable, albeit often imprecise, role in the genesis of the epilepsies (so-called cryptogenic epilepsy). Modern neuroimaging techniques reveal that many
<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Inheritance</th>
<th>Protein</th>
<th>Epilepsy syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALG13</td>
<td>Xq23</td>
<td>XL</td>
<td>Asparagine-linked glycosylation 13</td>
<td>West (congenital disorder of glycosylation Type 1s)</td>
</tr>
<tr>
<td>ARHGEF9</td>
<td>Xq11</td>
<td>XL</td>
<td>Rho-like GTPase</td>
<td>EIEE</td>
</tr>
<tr>
<td>ATP1A3</td>
<td>19q13.2</td>
<td>AD</td>
<td>ATPase, Na+/K+ transporting, alpha-3 polypeptide</td>
<td>EE, alternating hemiplegia of childhood, CAPOS, Dystonia 12</td>
</tr>
<tr>
<td>BRAT1</td>
<td>7p22.3</td>
<td>AR</td>
<td>BRCA1-associated ATM activator 1</td>
<td>Rigidity and multifocal seizure syndrome, lethal neonatal</td>
</tr>
<tr>
<td>BRD2</td>
<td>6p21</td>
<td>AD</td>
<td>Bromodomain-containing protein 2</td>
<td>JME (susceptibility to)</td>
</tr>
<tr>
<td>ARX</td>
<td>Xp21.3</td>
<td>XL</td>
<td>Aristless-related homeobox</td>
<td>EIEE, West syndrome</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>19p13.13</td>
<td>AD</td>
<td>Calcium channel, voltage-dependant, P/Q type, alpha 1A</td>
<td>EIEE, Episodic ataxia 2, familial hemiplegic migraine 1</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>Xp22.13</td>
<td>XL</td>
<td>Serine-threonine protein kinase</td>
<td>EIEE, West syndrome</td>
</tr>
<tr>
<td>CERS1</td>
<td>15q26.1</td>
<td>AD</td>
<td>Cystatin B</td>
<td>PME</td>
</tr>
<tr>
<td>CHD2</td>
<td>1q21.3</td>
<td>AD</td>
<td>Cystatin B</td>
<td>EEE</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>20q13.33</td>
<td>AD</td>
<td>Cholinergic receptor, neuronal nicotinic alpha polypeptide 4</td>
<td>NFLE</td>
</tr>
<tr>
<td>CHRNA2</td>
<td>8p21.2</td>
<td>AD</td>
<td>Cholinergic receptor, neuronal nicotinic alpha polypeptide b</td>
<td>NFLE</td>
</tr>
<tr>
<td>CHRNB2</td>
<td>1q21.3</td>
<td>AD</td>
<td>Cholinergic receptor, neuronal nicotinic beta polypeptide b</td>
<td>NFLE</td>
</tr>
<tr>
<td>CLCN2</td>
<td>3p26</td>
<td>AD</td>
<td>Chloride-channel 2</td>
<td>IGE</td>
</tr>
<tr>
<td>CSTB</td>
<td>21q22.3</td>
<td>AR</td>
<td>Cystatin C</td>
<td>Progressive myoclonic epilepsy 1A (Unverricht-Lundborg)</td>
</tr>
<tr>
<td>DEPDC5</td>
<td>22q11.2-q12.3</td>
<td>AD</td>
<td>DEP domain-containing protein 5</td>
<td>FFEV, NFLE</td>
</tr>
<tr>
<td>DNM1</td>
<td>9q34.11</td>
<td>AD</td>
<td>Dynamin 1</td>
<td>EE</td>
</tr>
<tr>
<td>DOCK7</td>
<td>1p31.3</td>
<td>AD</td>
<td>Dedicator of cytokinesis 7</td>
<td>EIEE</td>
</tr>
<tr>
<td>EF1A2</td>
<td>20q13.33</td>
<td>AD</td>
<td>Eukaryotic translation elongation factor 1 alpha 2</td>
<td>EIEE</td>
</tr>
<tr>
<td>EFHC1</td>
<td>6p12–p11</td>
<td>AD</td>
<td>EF-hand domain (C-terminal)-containing protein 1</td>
<td>JME (susceptibility to)</td>
</tr>
<tr>
<td>EPM2A</td>
<td>6q24.3</td>
<td>AR</td>
<td>Laforin</td>
<td>PME 2A (Lafora)</td>
</tr>
<tr>
<td>FRSS1L</td>
<td>9q31.3</td>
<td>AR</td>
<td>Ferric chelate reductase 1-like</td>
<td>EIEE</td>
</tr>
<tr>
<td>GABBR2</td>
<td>9q22.33</td>
<td>AD</td>
<td>Gamma-aminobutyric acid B receptor 2</td>
<td>EE</td>
</tr>
<tr>
<td>GABRA1</td>
<td>5q34</td>
<td>AD</td>
<td>Gamma-aminobutyric acid receptor, alpha 1</td>
<td>EIEE, JME (susceptibility to)</td>
</tr>
<tr>
<td>GABRB3</td>
<td>15q12</td>
<td>AD</td>
<td>Gamma-aminobutyric acid receptor, beta 3</td>
<td>EE</td>
</tr>
<tr>
<td>GABRD</td>
<td>1p36</td>
<td>AD</td>
<td>Gamma-aminobutyric acid receptor, delta</td>
<td>GEFS+</td>
</tr>
<tr>
<td>GABRG2</td>
<td>5q31</td>
<td>AD</td>
<td>Gamma-aminobutyric acid receptor, gamma 2</td>
<td>GEFS+, CAE</td>
</tr>
<tr>
<td>GNAO1</td>
<td>16q12.2</td>
<td>AD</td>
<td>Guanine nucleotide-binding protein alpha-activating activity polypeptide O</td>
<td>EIEE</td>
</tr>
<tr>
<td>GOSR2</td>
<td>17q21.32</td>
<td>AR</td>
<td>Golgi SNAP receptor complex member 2</td>
<td>PME</td>
</tr>
<tr>
<td>GRIN1</td>
<td>9q34.3</td>
<td>AD, AR</td>
<td>Glutamate receptor, ionotopic, N-methyl-D-aspartate subunit 1</td>
<td>EIEE</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Inheritance</th>
<th>Protein</th>
<th>Epilepsy syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRIN2A</td>
<td>16p13.2</td>
<td>AD</td>
<td>Glutamate receptor, ionotropic, N-methyl-D-aspartate subunit 2A</td>
<td>EE, epilepsy-aphasia syndrome</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>12p13.1</td>
<td>AD</td>
<td>Glutamate receptor, ionotropic, N-methyl-D-aspartate subunit 2B</td>
<td>EIEE, West</td>
</tr>
<tr>
<td>GRIN2D</td>
<td>19q13.33</td>
<td>AD</td>
<td>Glutamate receptor, ionotropic, N-methyl-D-aspartate subunit D</td>
<td>EIEE</td>
</tr>
<tr>
<td>HCN1</td>
<td>5p12</td>
<td>AD</td>
<td>Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1</td>
<td>EIEE</td>
</tr>
<tr>
<td>HDAC4</td>
<td>2q37.3</td>
<td>AD</td>
<td>Histone deacetylase 4</td>
<td>EE</td>
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<tr>
<td>IQSEC2</td>
<td>Xp11.22</td>
<td>XL</td>
<td>IQ motif- and SEC7 domain-containing protein 2</td>
<td>EE</td>
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<tr>
<td>KCNA2</td>
<td>1p13.3</td>
<td>AD</td>
<td>Potassium channel, voltage-gated, shaker-related subfamily, member 2</td>
<td>EIEE</td>
</tr>
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<td>KCNC1</td>
<td>11p15.1</td>
<td>AD</td>
<td>Potassium channel, voltage-gated, shaw-related subfamily, member 1</td>
<td>PME</td>
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<td>KCNJ10</td>
<td>1q23.2</td>
<td>AR</td>
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<tr>
<td>KCNMA1</td>
<td>10q22.3</td>
<td>AD</td>
<td>Potassium channel, calcium-activated, large conductance, subfamily M, alpha member 1</td>
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</tr>
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<td>KCNQ2</td>
<td>20q13.33</td>
<td>AD</td>
<td>Voltage-gated potassium channel</td>
<td>EIEE, BFNE</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>8q24</td>
<td>AD</td>
<td>Voltage-gated potassium channel</td>
<td>BFNE</td>
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<td>KCNT1</td>
<td>9q34.3</td>
<td>AD</td>
<td>Potassium channel subfamily T, member 1</td>
<td>EIEE, MPSI, NFLE</td>
</tr>
<tr>
<td>KCTD7</td>
<td>7q11.21</td>
<td>AR</td>
<td>Potassium channel tetramerization domain-containing protein 7</td>
<td>PME</td>
</tr>
<tr>
<td>LGII</td>
<td>10q23.33</td>
<td>AD</td>
<td>Leucine-rich gene, glioma-inactivated, 1</td>
<td>ADPEAF</td>
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<td>LMNB2</td>
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<td>AR</td>
<td>Lamin B</td>
<td>PME</td>
</tr>
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<td>MEF2C</td>
<td>5q14.3</td>
<td>AD</td>
<td>Mads Box Transcription Enhancer Factor 2</td>
<td>Intellectual disability, stereotypic movements, epilepsy</td>
</tr>
<tr>
<td>MTO1</td>
<td>1p36.22</td>
<td>AD</td>
<td>Mechanistic target of rapamycin</td>
<td>Focal cortical dysplasia and epilepsy, Smith-Kingsmore</td>
</tr>
<tr>
<td>NHRLC1</td>
<td>6p22.3</td>
<td>AR</td>
<td>NHL repeat-containing 1</td>
<td>PME 2B</td>
</tr>
<tr>
<td>NECAP1</td>
<td>12p13.31</td>
<td>AR</td>
<td>NECAP endocytosis-associated protein 1</td>
<td>EIEE</td>
</tr>
<tr>
<td>NPRL2</td>
<td>3p21.31</td>
<td>AD</td>
<td>NPR2-like protein, GATOR1 complex subunit</td>
<td>FFEV, NFLE</td>
</tr>
<tr>
<td>NPRL3</td>
<td>16p13.3</td>
<td>AD</td>
<td>NPR3-like protein, GATOR1 complex subunit</td>
<td>FFEV, NFLE</td>
</tr>
<tr>
<td>PCDH19</td>
<td>Xq22.1</td>
<td>XL (unusual)</td>
<td>Protocadherin 19</td>
<td>EIEE, epilepsy and intellectual disability limited to females</td>
</tr>
<tr>
<td>PIGA</td>
<td>Xp22.2</td>
<td>XL</td>
<td>Phosphatidylinositol glycan, class A</td>
<td>EIEE</td>
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<tr>
<td>PLCB1</td>
<td>20p12.3</td>
<td>AR</td>
<td>Phospholipase C-beta</td>
<td>EIEE</td>
</tr>
<tr>
<td>PNKP</td>
<td>19q13.33</td>
<td>AR</td>
<td>Polynucleotide kinase 3’phosphatase</td>
<td>EIEE</td>
</tr>
<tr>
<td>PNPO</td>
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<td>AR</td>
<td>Pyridoxamine 5’-phosphate oxidase</td>
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<tr>
<td>PRDM8</td>
<td>4q21.21</td>
<td>AR</td>
<td>PR domain-containing protein 8</td>
<td>PME</td>
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</table>

Table 16.2a  Identified genes for epilepsy per gene (continued)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Inheritance</th>
<th>Protein</th>
<th>Epilepsy syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRICKLE1</td>
<td>12q12</td>
<td>AR</td>
<td>Homologue of Prickle 1</td>
<td>PME 1B</td>
</tr>
<tr>
<td>QARS</td>
<td>3p21.31</td>
<td>AR</td>
<td>Glutaminyl-tRNA synthetase</td>
<td>Progressive microcephaly, seizures and cerebral/cerebellar atrophy</td>
</tr>
<tr>
<td>PRRT2</td>
<td>16p11.2</td>
<td>AD</td>
<td>Poline-rich transmembrane protein 2</td>
<td>BFIE, ICCA, kinesigenic dyskinesia</td>
</tr>
<tr>
<td>SCARB2</td>
<td>4q21.1</td>
<td>AR</td>
<td>Scavenger receptor class B, member 2</td>
<td>PME with or without renal failure</td>
</tr>
<tr>
<td>SCN1A</td>
<td>2q24.3</td>
<td>AD</td>
<td>Voltage-gated sodium channel</td>
<td>EIEE, Dravet, GEFS+</td>
</tr>
<tr>
<td>SCN1B</td>
<td>19q13.33</td>
<td>AD (AR?)</td>
<td>Voltage-gated sodium channel</td>
<td>GEFS+ (Dravet?)</td>
</tr>
<tr>
<td>SCN2A</td>
<td>2q24.3</td>
<td>AD</td>
<td>Voltage-gated sodium channel</td>
<td>EIEE, BFNE</td>
</tr>
<tr>
<td>SCN8A</td>
<td>12q13.13</td>
<td>AD</td>
<td>Sodium channel, voltage-gated, Type VIII, alpha subunit</td>
<td>EIEE, BFNE</td>
</tr>
<tr>
<td>SLC12A5</td>
<td>20q13.12</td>
<td>AR</td>
<td>Solute carrier family 12 (potassium/chloride transporter), member 5</td>
<td>EIEE</td>
</tr>
<tr>
<td>SLC13A5</td>
<td>17p13.1</td>
<td>AR</td>
<td>Solute carrier family 13 (sodium-dependent citrate transporter) member 5</td>
<td>EIEE</td>
</tr>
<tr>
<td>SLC25A22</td>
<td>11p15.5</td>
<td>AR</td>
<td>Mitochondrial metabolic transporter</td>
<td>EIEE</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>1p34.2</td>
<td>AD</td>
<td>Solute carrier family 2 (facilitated glucose transporter) member 1, GLUT1</td>
<td>GLUT1 deficiency</td>
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<td>SLC35A2</td>
<td>Xp11.23</td>
<td>XL</td>
<td>Solute carrier family 35 (UDP-Galactose transporter) member 2</td>
<td>EIEE</td>
</tr>
<tr>
<td>SLC6A1</td>
<td>3p25.3</td>
<td>AD</td>
<td>Solute carrier family 6 (GABA transporter) member 1</td>
<td>Myoclonic-atonic epilepsy</td>
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<td>SLC9A6</td>
<td>Xq26.3</td>
<td>XL</td>
<td>Solute carrier family 9, member 6</td>
<td>Christianson syndrome</td>
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<tr>
<td>SPTAN1</td>
<td>9q34.11</td>
<td>AD</td>
<td>Alpha-spectrin-1</td>
<td>EIEE</td>
</tr>
<tr>
<td>ST3GAL3</td>
<td>1p34.1</td>
<td>AR</td>
<td>ST3-galactoside alpha-2, 3-sialyltransferase 3</td>
<td>EIEE</td>
</tr>
<tr>
<td>STXB1P1</td>
<td>9q34.11</td>
<td>AD</td>
<td>Syntaxin-binding protein 1 (SNARE)</td>
<td>EIEE, West</td>
</tr>
<tr>
<td>SYN1</td>
<td>Xp11.23</td>
<td>XL</td>
<td>Synapsin 1</td>
<td>Focal epilepsy with learning disabilities</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>6p21.32</td>
<td>AD</td>
<td>Synaptic Ras-GTPase-activating protein 1</td>
<td>EE</td>
</tr>
<tr>
<td>SZT2</td>
<td>1p34.2</td>
<td>AR</td>
<td>Seizure threshold 2, mouse homologue</td>
<td>EIEE</td>
</tr>
<tr>
<td>TBC1D24</td>
<td>16p13.3</td>
<td>AR</td>
<td>TBC1 domain family, member 24</td>
<td>EIEE, Familial infantile myoclonic epilepsy, DOORS</td>
</tr>
<tr>
<td>TNK2</td>
<td>3q29</td>
<td>AR</td>
<td>Tyrosine kinase, nonreceptor 2</td>
<td>Severe autosomal recessive infantile onset epilepsy</td>
</tr>
<tr>
<td>UBA5</td>
<td>3q22.1</td>
<td>AR</td>
<td>Ubiquitin-like modifier activating enzyme 5</td>
<td>EIEE</td>
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<tr>
<td>WWOX</td>
<td>16q23.1-q23.2</td>
<td>AR</td>
<td>WW domain-containing oxidoreductase</td>
<td>Cerebellar ataxia with epilepsy and intellectual disability</td>
</tr>
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</table>

Table 16.2a: Identified genes for epilepsy per gene (continued)

Modified from Arzimanoglou et al. (2004), Guerrini (2006). (Courtesy Professor G Lesca, University Hospitals of Lyon, France).

XL, X-linked; AD, autosomal dominant; AR, autosomal recessive; EIEE, early infantile epileptic encephalopathy; EE, epileptic encephalopathy; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensoryneural hearing loss; JME, juvenile myoclonic epilepsy; PME, progressive myoclonic epilepsy; NFLE, nocturnal frontal-lobe epilepsy; IGE, idiopathic generalised epilepsy; FFVE, familial focal epilepsy with variable foci; BFNE, benign familial neonatal epilepsy; MPSIE, migrating partial seizures of infancy; BFIE, benign familial infantile epilepsy; ICCA, (familial) infantile convulsions with paroxysmal choroidoretinopathy; GEFS+, generalised (or genetic) epilepsy with febrile seizures plus; BFNIE, benign familial neonatal infantile epilepsy; CAE, childhood absence epilepsy; DOORS, deafness, onychodystrophy, osteodystrophy, intellectual disability and seizures.
Table 16.2b  Identified genes per epilepsy syndrome

<table>
<thead>
<tr>
<th>Epilepsy syndromes and epilepsies</th>
<th>Reported genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity and multifocal seizure syndrome, lethal neonatal</td>
<td>BRAT1</td>
</tr>
<tr>
<td>Early infantile epileptic encephalopathy</td>
<td>ARHGEF9, ARX, CACNA1A, CDKL5, DOCK7, EEF1A2, FRRS1L, GABRA1, GNAO1, GRIN1, GRIN2B, GRIN2D, HCN1, KCNA1, KCNQ2, KCNT1, NECAP1, PCDH19, PIGA, PLCB1, PNPK, PNPO, SCN1A, SCN2A, SCN8A, SLC12A5, SLC13A5, SLC25A22, SLC35A2, SPTAN1, ST3GAL3, STXBPI, S1T2, TBC1D24, UBA5</td>
</tr>
<tr>
<td>Benign familial neonatal epilepsy</td>
<td>KCNQ2, KCNQ3</td>
</tr>
<tr>
<td>Benign familial neonatal infantile epilepsy</td>
<td>SCN2A</td>
</tr>
<tr>
<td>Benign familial infantile epilepsy (=+/- ICCA, kinesigenic dyskinesia)</td>
<td>PRR72, SCN8A</td>
</tr>
<tr>
<td>Familial infantile myoclonic epilepsy</td>
<td>TBC1D24</td>
</tr>
<tr>
<td>Infantile epileptic spasms/West syndrome</td>
<td>ALG13, ARX, CDKL5, GRIN2B, STXBPI, MEF2C, SCN1A, SCN2A, DEPDC5, KCNQ2</td>
</tr>
<tr>
<td>Migrating partial seizures of infancy</td>
<td>KCNT1, TBC1D24, SCN2A, SCN1A, SCN8A, SLC12A5</td>
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<tr>
<td>Epileptic encephalopathy</td>
<td>ATP1A3, CHD2, DNM1, GABBR2, GABRG2, GABRB3, GRIN2A, HDAC4, IQSEC2, QARS, SYNGAP1, TNK2, WWOX</td>
</tr>
<tr>
<td>SESAME syndrome</td>
<td>KCNJ10</td>
</tr>
<tr>
<td>Generalised epilepsy with febrile seizures, plus</td>
<td>SCN1A, SCN1B, GABRG2, GABRD, STX1B</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>SCN1A, SCN1B, HCN1, CHD2</td>
</tr>
<tr>
<td>GLUT1 deficiency</td>
<td>SLC2A1</td>
</tr>
<tr>
<td>Epilepsy-aphasia syndrome (Landau-Kleffner)</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>Myoclonic-atactic epilepsy</td>
<td>SLC6A1, SYNGAP1, GABRB3</td>
</tr>
<tr>
<td>Generalised epilepsy and paroxysmal dyskinesia</td>
<td>KCNMA1</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsies</td>
<td>CERS1, CSTB, EPM2A, NHLRC1, GOSR2, KCNC1, KCTD7, LMRNB2, PRDM8, SCARB2, PRICKLE1</td>
</tr>
<tr>
<td>Nocturnal frontal lobe epilepsies (NFLE)</td>
<td>CHRNA4, CHRNA2, CHRN8B2, KCNT1</td>
</tr>
<tr>
<td>Familial focal epilepsy with variable foci (FFEV); NFLE</td>
<td>DEPDC5, NPRL2, NPRL3</td>
</tr>
<tr>
<td>ADPEAF</td>
<td>LG11</td>
</tr>
<tr>
<td>Focal cortical dysplasia and epilepsy, Smith-Kingsmore</td>
<td>MTOR</td>
</tr>
<tr>
<td>Christiansen syndrome</td>
<td>SLC9A6</td>
</tr>
<tr>
<td>Focal epilepsy with learning disabilities</td>
<td>SYN1</td>
</tr>
</tbody>
</table>

Modified from Arzimanoglou et al. (2004), Guerrini (2006). (Courtesy Professor G Lesca, University Hospitals of Lyon, France.)

ICCA, infantile convulsions and choreoathetosis; ADPEAF, autosomal dominant partial epilepsy with auditory features.

PATHOLOGY

Epileptic seizures (and epilepsy) occur in patients with many pathological processes including brain malformations, tumours, acquired traumatic or vascular lesions (Blümcke et al. 2015). An important issue is whether lesions found in patients with epileptic seizures are the cause or the consequences of the epileptic activity. Whether lesions remain stable or are
Chapter 16 Epilepsy and Other Seizure Disorders

worsened by recurrent seizures is also unknown. Prognosis and therapeutic attitudes often depend critically on answers to these questions. The respective roles of the original lesion and of lesions resulting from the epileptic activity itself are still debated (Fuerst et al. 2003; Armstrong 2005; Bernasconi et al. 2005). Some investigators minimise the role of seizures (Lado et al. 2002), while others suggest that both experimental and clinical evidence favour the importance of epilepsy not only on structural brain damage but also on the propensity to seizure repetition and cognitive and behavioural development (Sutula 2004).

Two major types of pathological abnormalities occur in patients with focal epilepsy: developmental cortical malformations, and acquired lesions, the commonest being hippocampal (or mesial temporal) here.

Hippocampal sclerosis is characterised by marked neuronal loss in the CA1 sector of the hippocampus, with a lesser degree of cell loss in the CA3/CA4 sectors and a relative sparing of the CA2 region (Fig. 16.3a, b). Recent data suggest that the pattern of cell loss in the hippocampus is distinct from hippocampal sclerosis associated with other neocortical temporal lobe pathologies (so-called dual pathology cases), showing a trend toward more diffuse and homogeneous neuronal loss in all hippocampal sectors (Diehl et al. 2002).

The term ‘mesial temporal sclerosis’ is often used synonymously but in fact designates more extensive involvement of the internal temporal lobe. Over the past decades, there have been various attempts to classify specific patterns of hippocampal neuronal cell loss and correlate subtypes with postsurgical outcome.

In 2013, the ILAE published an international consensus classification of hippocampal sclerosis (Blümcke et al. 2013). HS-ILAE Type 1 refers always to severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions, compared to CA1 predominant neuronal cell loss and gliosis (HS-ILAE Type 2), or CA4 predominant neuronal cell loss and gliosis (HS-ILAE Type 3). Surgical hippocampus specimens obtained from patients with temporal lobe epilepsy (TLE) may also show normal content of neurons with reactive gliosis only (no-HS). According to this report (Blümcke et al. 2013) HS-ILAE Type 1 is more often associated with a history of initial precipitating injuries before age 5 years, with early seizure onset, and favourable postsurgical seizure control. CA1 predominant HS-ILAE Type 2 and CA4 predominant HS-ILAE Type 3 have been studied less systematically so far, but some reports point to less favourable outcome, and to differences regarding epilepsy history, including age of seizure onset.

There is resulting gliosis and atrophy and, in patients with epilepsies dating back to infancy or early childhood, especially those that follow prolonged febrile seizures (Sagar and Oxbury 1987; Sutula et al. 1989; Mathern et al. 1996), sprouting of the mossy fibres is prominent and results in new synaptic contacts being established (for a review, see Najm et al. 2006a).

Table 16.3 Aetiological factors of epilepsies due to brain damage

<table>
<thead>
<tr>
<th>Prenatal factors</th>
<th>Infections (toxoplasmosis, cytomegalovirus, rubella, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consequences of some metabolic disorders (maternal diabetes, maternal phenylketonuria)</td>
</tr>
<tr>
<td></td>
<td>Haemorrhages (rare, due to platelet isoimmunisation, etc.)</td>
</tr>
<tr>
<td></td>
<td>Vascular malformations, esp. cavernomas</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perinatal factors</th>
<th>Infections (purulent meningitis, viral encephalitis, brain abscess)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemorrhage (intraparenchymal, subdural, subarachnoid, intraventricular)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Hypoxic–ischaemic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Metabolic or toxic (hypocalcaemia, hypoglycaemia, hyponatraemia)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postnatal factors</th>
<th>Infections and parasitic lesions, e.g. cysticercosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postnatal hypoxia (near-drowning, cardiac arrest)</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Consequences of prolonged convulsive seizures (convulsive status epilepticus, hiconvulsions–hemisegia–epilepsy syndrome)</td>
</tr>
</tbody>
</table>
Whether hippocampal sclerosis is a cause or a consequence of repetitive or prolonged epileptic seizures is still debated (Bruton 1988; Liu et al. 1995; de Lanerolle and Lee 2005); evidence exists in favour of the latter hypothesis (Meldrum 1978). Excessive release of excitatory amino acids (glutamate) at the synapses has been shown to produce excitotoxic hippocampal damage in experimental conditions. Nerve cell death due to excessive activation (burst firing) probably results because of increase in intracellular calcium entry through N-methyl-D-aspartate (NMDA) receptors and some AMPA receptors, when the capacity of calcium-buffering proteins in postsynaptic cells is limited. This is the case in the CA1 and CA3 sectors of the hippocampus.

Even in the absence of microscopic lesions, there is evidence that seizures in infancy create lasting hyperexcitability of neuronal assemblies and favour the occurrence of later seizures (Baram 2003).

**Abnormalities of cortical development** (Table 16.4; also refer to Chapter 3) are recognised as a major cause of both epilepsies and developmental disabilities (Raymond et al. 1995; Guerini et al. 1996; Arzimanoglou et al. 2004; Guerrini and Filippi 2005). Until the advent of high-resolution neuroimaging, these abnormalities were the domain of the pathologists, but they can now be detected more reliably with high-resolution magnetic resonance imaging (MRI). Some are genetically determined, while for others a genetic origin is only hypothesised (Guerini and Carrozzo 2001; Dobyns and Kuzniecky 2006).

New data from MRI studies and the discovery of specific genetic mutations underlying some of these abnormalities have led to the development of various classifications based on morphological, anatomical or genetic characteristics (Sarnat and Flores-Sarnat 2004; Palmini et al. 2004; Barkovich et al. 2005). All have some practical value for the clinician, but the complexity of the issues makes it impossible for any one classification scheme to cover all aspects (clinical, radiological, aetiological and treatment). Furthermore, all classifications need to be regularly updated as much remains to be discovered in this rapidly expanding field (for reviews see Vigevano et al. 2003; Arzimanoglou et al. 2004; Sisodiya 2004; Blümcke et al. 2011, 2015).

**Diffuse abnormalities of cortical development** are usually the cause of severe and early-onset epilepsy, intellectual disability and intractability. However, some abnormalities, such as bilateral periventricular heterotopias, may be asymptomatic or associated with a relatively mild epilepsy phenotype. Focal cortical developmental anomalies are usually revealed by epilepsy, whether or not they are associated with cognitive problems. They represent one of the most frequent causes of non-idiopathic (structural) focal epilepsies. Following the recent development of high-resolution magnetic resonance neuroimaging, many ‘cryptogenic focal epilepsies’ are now recognised as being ‘symptomatic’ of cortical maldevelopment. Since the original description by Taylor et al. (1971), the term *focal cortical dysplasia* (FCD) is used to refer to a wide range of alterations of the cortical mantle.

Several classification schemes have been introduced. A proposal by Barkovich et al. (2005) was based more on genotype than phenotype. However, the genotype–phenotype relationship is incompletely understood for many abnormalities. A simplified classification referring to easily recognised neuropathological characteristics (Tassi et al. 2002) was based upon the identification of three subgroups: (1) architectural dysplasia characterised by abnormal cortical lamination and ectopic neurons in white matter; (2) cytoarchitectural dysplasia characterised by giant neurofilament-enriched neurons in addition to altered cortical lamination; and (3) Taylor-type cortical dysplasia with giant dysmorphic neurons and

---

**Figure 16.3**
(a) Schematic distribution of Ammon horn sectors. (b) Hippocampal sclerosis Type 2 (ILAE classification 2013) in a male patient with right temporal lobe epilepsy since age 12 years. NeuN-immunohistochemistry shows predominant segmental (pyramidal) cell loss in CA1 (see higher magnification at lower left. SUB, subiculum; ECx, cortex entorhinalis; GC, granule cells of dentate gyrus. Scale bar = 1mm. (Courtesy Professor Ingmar Blümcke, Erlangen, Germany.)
Table 16.4 Abnormalities of cortical development and epilepsy

<table>
<thead>
<tr>
<th>DIFFUSE OR HEMISPHERIC</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lissencephaly</td>
<td></td>
</tr>
<tr>
<td>Hemimegalencephaly</td>
<td></td>
</tr>
<tr>
<td>Subcortical band heterotopia</td>
<td></td>
</tr>
<tr>
<td>Polymicrogyria (of variable extent and location)</td>
<td></td>
</tr>
<tr>
<td>Bilateral perisylvian polymicrogyria</td>
<td></td>
</tr>
<tr>
<td>Bilateral parasagittal parieto-occipital polymicrogyria</td>
<td></td>
</tr>
<tr>
<td>Bilateral periventriculal nodular heterotopias</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FOCAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>According to Tassi et al. 2002</td>
<td></td>
</tr>
<tr>
<td>Architectural dysplasia (abnormal cortical lamination and ectopic neurons in white matter)</td>
<td></td>
</tr>
<tr>
<td>Cytoarchitectural dysplasia (giant neurofilament-enriched neurons and altered cortical lamination)</td>
<td></td>
</tr>
<tr>
<td>Taylor-type (with giant dysmorphic neurons and balloon cells associated with cortical laminar disruption)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FOCAL CORTICAL DYSPLASIAS (FCD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FCD Type I (isolated)</td>
<td></td>
</tr>
<tr>
<td>Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)</td>
<td></td>
</tr>
<tr>
<td>Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)</td>
<td></td>
</tr>
<tr>
<td>Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FCD Type II (isolated)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)</td>
<td></td>
</tr>
<tr>
<td>Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCD Type III (associated with principal lesion)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)</td>
<td></td>
</tr>
<tr>
<td>Cortical lamination abnormalities adjacent to a glial or glioneuronal tumour (FCD Type IIIb)</td>
<td></td>
</tr>
<tr>
<td>Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)</td>
<td></td>
</tr>
<tr>
<td>Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g. trauma, ischaemic injury, encephalitis (FCD Type IIId)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCD Type III (not otherwise specified)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If clinically/radiologically suspected principal lesion is not available for microscopic inspection.</td>
<td></td>
</tr>
</tbody>
</table>

The rare association between FCD Types IIa and IIb and hippocampal sclerosis, tumours or vascular malformations should not be classified as FCD Type III variant.

balloon cells associated with cortical laminar disruption. Patients with architectural dysplasia have lower seizure frequencies than those with cytoarchitectural and Taylor-type dysplasia, and the epileptogenic zone is mainly in the temporal lobe. Surgical resection, when feasible, controls seizures in a substantial proportion of cases (Palmini et al. 1991; Chassoux et al. 2000; Tassi et al. 2002; Francione et al. 2003; Russo et al. 2003; Lawson et al. 2005; Tassi et al. 2010). In the series reported by Tassi et al. (2002), patients with Taylor-type dysplasia had the best outcome, with 75% seizure-freedom (Engel class Ia), despite the epileptogenic zone being mainly extratemporal. Seizure semiology depended on the location of the lesion, and patients with both Type I and Type II dysplasias both present high seizure frequencies (Tassi et al. 2010).

The subsequent introduction of the Palmini et al. (2004) classification of cortical dysplasias was widely used. In this schema, FCDs were histopathologically subdivided into Types I and II. FCD Type IA referred to architectural disturbances of cortical lamination, and FCD Type IB included cytoarchitectural abnormalities, including hypertrophic (not dysmorphic) pyramidal neurons outside layer 5. Dysmorphic neurons were considered the histopathologic hallmark of FCD Type IIA. Microscopic identification of dysmorphic neurons and eosinophilic balloon cells defined FCD Type IIB.

In 2011, an ad hoc ILAE Task Force reviewed available literature on clinical presentation, imaging findings, and histopathological features of distinct clinico-pathologic FCD variants (Fig. 16.4) and proposed a refined classification system (Blümcke et al. 2011). Accordingly, FCD Type I refers to isolated lesions, which present either as radial (FCD Type Ia) or tangential (FCD Type Ib) dyslaminations of the neocortex, microscopically identified in one or multiple lobes. FCD Type II is an isolated lesion characterised by cortical
Part VII Paroxysmal Disorders

Dyslamination and dysmorphic neurons without (Type IIa) or with balloon cells (Type IIb). Hence, the major change was the introduction of FCD Type III, which occurs in combination with hippocampal sclerosis (FCD Type IIIa), or with epilepsy-associated tumours (FCD Type IIIb). FCD Type IIIc is found adjacent to vascular malformations, whereas FCD Type IIIId can be diagnosed in association with epileptogenic lesions acquired in early life (i.e. traumatic injury, ischaemic injury or encephalitis).

The diagnosis of a cortical development disorder, and identification of the initial abnormality type, is essential because an increasing number of genetically transmitted forms are known. In patients with drug-resistant focal seizures MRI investigations should be repeated, if possible using higher resolution scanners, because in a significant proportion of patients the brain appears morphologically normal on routine scanning (MRI was unrevealing in 34% of the patients reported by Tassi et al. 2002). Information on the suspected localisation, based on careful analysis of clinical semiology and video-EEG data, has to be provided to the neuroradiologist, who preferably should review the MRI in close collaboration with the epilepsy team at multidisciplinary sessions.

Figure 16.4 Variable patterns of abnormal cortical architecture in surgical focal cortical dysplasia (FCD) specimens. (a) shows excessive radial microcolumns (arrow) in a child with early seizure onset in the left posterior quadrant. (b) FCD IIa is characterised by architectural layer abnormalities (arrow) and large dysmorphic neurons. (c) FCD IIa in the temporal lobe of a patient with hippocampal sclerosis (associated FCD). Note neuronal depletion in layer 2 (arrow) in an otherwise normally developed six-layered neocortex. (Courtesy Professor, Ingmar Blümcke, Erlangen, Germany.)

Classification Issues

Because epileptic seizures are a symptom of multiple disorders, a single classification code is not possible. Criteria need also to be pre-established when classifying epilepsies, which also correspond to a great variety of diseases. Several classification systems can be utilised at different levels (e.g. aetiological, topographic, neurophysiological, etc.). Clinical classifications have received special attention for communicative, diagnostic and prognostic purposes (for a critical review of the nosological approach to the epilepsies, from prehistoric times to the present, and a highlight on how these views are reflected by terminology and classification see Wolf 2014).

The ILAE has devised two classification schemes: one for epileptic seizures only, the other for epilepsies and epilepsy syndromes. Both evolved with time on the basis of acquired new knowledge, usually also respecting evolution of practices.

Classification of Epileptic Seizures

The 1969 and the revised (1989) ILAE classifications of epileptic seizures were based on clinical seizure type and EEG findings; the major distinction was between partial (focal) seizures in which the first clinical symptoms indicate ‘activation of an anatomico-functional system of neurons limited to a part of a single hemisphere’, and generalised seizures in which the first electroclinical changes indicate involvement of both hemispheres with further subdivisions (Table 16.5). This classification requires acceptance of concepts that are not universally accepted, especially with respect to generalised seizures. Separating seizures as generalised or focal is often challenging, as the concept of seizures involving homogeneously the entire cortex is untenable (see Hirsch et al. 2006a), and differentiation of secondarily generalised seizures of focal origin from generalised seizures is not always possible in clinical practice. However, seizure onset classification is important practically because treatment may not be the same and only focal seizures are amenable to surgical resective treatment.

In 1999, a conceptually different system for seizure classification was proposed (Lüders et al. 1999) (Table 16.6) based entirely on clinical description of the ictal events (phenomenology), and provided a systematic list for the clinical analysis of the seizures, thus avoiding any assumptions regarding mechanisms and causes. It is applicable to infants and young children as only objective phenomena are listed. Following publication this proposal influenced the official ILAE classifications but was not widely accepted by the epilepsy community. It is mainly used by teams practising epilepsy surgery due to the need for detailed clinical observation and description of clinical events.

The 2006 ILAE report (Engel 2006) admitted the criticisms based on the artificial dichotomy of focal (partial) versus generalised origin of epileptic seizures but also recognised the practical value of distinguishing epileptic seizures that appear to begin in a region of one hemisphere, from those beginning in both hemispheres apparently simultaneously. Given
<table>
<thead>
<tr>
<th>Clinical seizure type</th>
<th>EEG patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARTIAL SEIZURES</strong></td>
<td>Local contralateral discharge starting over the corresponding area of cortical representation (not always recorded on scalp)</td>
</tr>
<tr>
<td><strong>Simple partial seizures</strong></td>
<td></td>
</tr>
<tr>
<td>With motor signs</td>
<td></td>
</tr>
<tr>
<td>Focal motor with march (jacksonian)</td>
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<tr>
<td>Focal motor without march</td>
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</tr>
<tr>
<td>Versive</td>
<td></td>
</tr>
<tr>
<td>Postural</td>
<td></td>
</tr>
<tr>
<td>Phonatory (vocalisation or arrest of speech)</td>
<td></td>
</tr>
<tr>
<td>With somatosensory or special sensory symptoms</td>
<td></td>
</tr>
<tr>
<td>Somatosensory</td>
<td></td>
</tr>
<tr>
<td>Visual, auditory, olfactory</td>
<td></td>
</tr>
<tr>
<td>Gustatory vertiginous</td>
<td></td>
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<tr>
<td>With autonomic symptoms</td>
<td></td>
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<tr>
<td>With psychic symptoms</td>
<td></td>
</tr>
<tr>
<td>Dysphasic</td>
<td></td>
</tr>
<tr>
<td>Dysmnesic (déjà vu, jamais vu)</td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td></td>
</tr>
<tr>
<td>Affective</td>
<td></td>
</tr>
<tr>
<td>Experiential (complex) hallucinations</td>
<td></td>
</tr>
<tr>
<td><strong>Complex partial seizures</strong></td>
<td>Unilateral or often bilateral discharge diffuse or focal over frontal and/or temporal regions</td>
</tr>
<tr>
<td>Simple partial onset followed by impairment of consciousness</td>
<td></td>
</tr>
<tr>
<td>With simple partial features</td>
<td></td>
</tr>
<tr>
<td>With automatisms</td>
<td></td>
</tr>
<tr>
<td>With impairment of consciousness from onset</td>
<td></td>
</tr>
<tr>
<td>Impairment of consciousness only</td>
<td></td>
</tr>
<tr>
<td>With automatisms</td>
<td></td>
</tr>
<tr>
<td><strong>Partial seizures evolving to secondarily generalised seizures</strong></td>
<td></td>
</tr>
<tr>
<td>Simple partial seizures</td>
<td></td>
</tr>
<tr>
<td>Complex partial seizures</td>
<td></td>
</tr>
<tr>
<td><strong>GENERALISED SEIZURES (convulsive or nonconvulsive)</strong></td>
<td></td>
</tr>
<tr>
<td>Absence seizures</td>
<td>Bursts of symmetrical rhythmic 3Hz spike-waves</td>
</tr>
<tr>
<td>Impairment of consciousness only</td>
<td></td>
</tr>
<tr>
<td>With mild clonic components</td>
<td></td>
</tr>
<tr>
<td>With atonic components</td>
<td></td>
</tr>
<tr>
<td>With tonic components</td>
<td></td>
</tr>
<tr>
<td>With automatisms</td>
<td></td>
</tr>
<tr>
<td>With autonomic components</td>
<td></td>
</tr>
<tr>
<td>Atypical absence seizures</td>
<td></td>
</tr>
<tr>
<td>With changes in tone more pronounced</td>
<td></td>
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<tr>
<td>Onset/cessation not abrupt</td>
<td></td>
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</tbody>
</table>

*Continued*
### Table 16.5  First International classification of epileptic seizures (continued)

<table>
<thead>
<tr>
<th>Clinical seizure type</th>
<th>EEG patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonic seizures</td>
<td>Polyspike and wave or spike-and-wave or sharp and slow wave</td>
</tr>
<tr>
<td>Clonic seizures</td>
<td>Fast activity (&gt;10Hz) and slow waves</td>
</tr>
<tr>
<td>Tonic seizures</td>
<td>Low voltage fast activity or fast (10Hz rhythm)</td>
</tr>
<tr>
<td>Tonic–clonic seizures</td>
<td>10Hz rhythm progressively slowed and intermingled with slow wave during clonic phase</td>
</tr>
<tr>
<td>Atonic seizures</td>
<td>As in tonic seizures</td>
</tr>
</tbody>
</table>

**UNCLASSIFIED SEIZURES**

Modified from the Commission on Classification (1981) of the International League Against Epilepsy.

### Table 16.6  The 'Lüders' classification of epileptic seizures

| Aura (consists exclusively of subjective symptoms) |
| Somatomotor\*                                      |
| Auditory\* (includes complex hallucinations and illusions that affect other senses) |
| Olfactory                                          |
| Visual\* (includes complex multimodal hallucinations) |
| Gustatory                                          |
| Autonomic\* (purely subjective autonomic sensations) |
| Psychic (includes complex hallucinations and illusions that affect other senses) |
| Abdominal aura                                     |

**Autonomic seizures** (only with objective autonomic dysfunction)

**Dialeptic seizures**\* (alteration of consciousness, whatever electroencephalogram and mechanism)

**Motor seizures**

Simple motor\* (unnatural movements resembling those produced by stimulation of areas 4 or 6)

Myoclonic seizures\*

Epileptic spasms\* (may occur after infancy)

Tonic–clonic seizures

Tonic seizures\*

Clonic seizures\*

Versive seizures\* (contralateral or ipsilateral)

Complex motor\* (refers to movements that simulate natural movements)

Hypermotor\* (complex mostly proximal, often violent)

Automotor\* (refers to mostly distal, mouth or tongue, consciousness variable)

Gelastic (those that cannot be included in the aforementioned categories)

**Special seizures**

Atonic\* (often preceded by short myoclonic seizure)

Hypomotor\* (decreased or total absence of motor activity; only when consciousness not assessable)

Negative myoclonus\*

Astatic

Akinetic\* (inability to perform voluntary movement) Aphasic\*

Paroxysmal events (not sufficient evidence to assume epileptic nature)


\*May be localised to left or right, axial, generalised, bilateral asymmetrical.

\*May arise from left or right hemisphere.

The term **dialeptic** was proposed in replacement of both ‘typical’ and ‘atypical’ absences on the basis that the distinction is possible on the basis of EEG data and/or the presence of other seizure types, clinical expression differences being often minimal.
the prevalent usage, and the therapeutic implications of the terms ‘focal’ and ‘generalised’, it was decided to retain them, with the understanding that the former does not necessarily imply that the epileptogenic region is limited to a small circumscribed area, while the latter does not imply that the entire brain is involved in the initiation of the epileptogenic process.

Four years later, the ad hoc ILAE Commission published a ‘revised terminology’ (Berg et al. 2010) that suggested the following changes to the 1981 classification:

1. Neonatal seizures were no longer a separate entity as seizures in neonates can be classified within the proposed general scheme. Although many paroxysmal manifestations can be documented in neonates, the practicing clinician is at risk to classify most symptoms as just ‘unknown’.
2. The previous sub-classification of absence seizures was simplified and altered. Myoclonic absence seizures and eyelid myoclonia were recognised.
3. Spasms, that were not explicitly acknowledged in the 1981 classification of seizures and considered as ‘generalised’ in the 2006 revision were re-classified as ‘epileptic spasms’ and grouped as ‘unknown’ in origin.
4. The distinction between ‘complex’ and ‘simple’ was eliminated for focal seizures and a list of ‘descriptors’ according to the degree of impairment was suggested.
5. The term ‘myoclonic–atonic’ replaced ‘myoclonic–astatic’.

The authors of the present chapter strongly believe that seizure classification is necessary and useful in everyday clinical practice. However, in comparison to the first ILAE classification (1981), the differences in the two that followed (Table 16.7) are minimal and have little impact on clinical practice; particularly when one considers the lengthy workshops needed to produce them and the confusion for those not in the epilepsy field. We believe revision is only justified when new, evidence-based data becomes available.

The latest revised operational classification of seizure types was published in 2017 as an ILAE position report (Fisher et al. 2017a) and was accompanied by an instruction manual (Fisher et al. 2017b). According to the authors, the main purpose of such a revision was to recognise that some seizure types can have either a focal or generalised onset, to allow classification when the onset is unobserved, to include some missing seizure types, and to adopt more transparent names. It also acknowledged that ‘because current knowledge is insufficient to form a scientifically based classification’, the one proposed should be considered ‘operational (practical) and based on the 1981 Classification, extended in 2010’.

Changes include the following:

1. ‘Partial’ becomes ‘focal’;
2. Awareness is used as a classifier of focal seizures;
3. The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalised are eliminated;
4. New focal seizure types include automatisms, behaviour arrest, hyperkinetic, autonomic, cognitive, and emotional;
5. Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalised onset;
6. Focal to bilateral tonic–clonic seizure replaces secondarily generalised seizure;
7. New generalised seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic; and
8. Seizures of unknown onset may have features that can still be classified.

The ILAE Task Force recognised that the new classification does not represent a fundamental change, but allows greater flexibility and transparency in naming seizure types. We agree that the 2017 version better reflects the needs of clinicians. It allows a description of the ictal pattern in individual patients. The level of description depends upon available information on the sequence of clinical manifestations (see also Lüders proposal in Table 16.6). It is enriched with time as more details become available (better description from the family and/or the patient; home videos; video-EEG data).

**CLASSIFICATION OF EPILEPSY SYNDROMES**

Progress in epileptology made it rapidly clear that, although crucial, the description of epileptic seizures was not sufficient to allow choice of investigation tools and treatment attitudes or to provide patients and families with a clear prognosis. The concept of epilepsy syndromes was introduced, defined as ‘clusters of signs and symptoms customarily occurring together’ (Commission on Classification and Terminology 1989).

The classification of 1989 (Table 16.8) was mainly based on the clinical and EEG characteristics of epilepsy syndromes (refer also to Koutroumanidis et al. 2017a,b). In addition to the descriptive elements of the clinical phenomena (seizures), it was considered that a classification of epilepsies should incorporate some information about the cause of the disorder, age at occurrence, features associated with the seizures, localisation and other aspects. However, any classification system must be understood as a compromise between the needs of the user and available knowledge. Often, a classification that is adapted to the needs of the neurosurgeon (type and localisation of an epileptogenic lesion), or to an epidemiologist (underlying aetiology or outcome) do not coincide with the goals of the basic scientist, geneticist, epileptologist, neurologist or general practitioner. In fact, no classification system can incorporate all possible issues related to such a complex and multifactorial disorder as epilepsy.

The ILAE system classified epilepsy syndromes according not only to their ictal phenomenology (clinical and EEG) but also to aetiology (idiopathic, symptomatic and cryptogenic syndromes) and mechanisms or topography (generalised, localisation-related, undetermined whether focal or generalised, and special or situation-related). The term ‘idiopathic’ includes syndromes in which epilepsy is not caused by a postnatally-acquired lesion or brain damage;
### Table 16.7  Comparison of the 2006 and 2010 ILAE revisions of the 1981 classification of seizures

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>I. Generalised onset</td>
<td>Generalised seizures</td>
</tr>
<tr>
<td>A. Seizures with tonic and/or clonic manifestations</td>
<td>1. Tonic–clonic seizures</td>
<td>Tonic–clonic (in any combination)</td>
</tr>
<tr>
<td></td>
<td>2. Clonic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Tonic seizures</td>
<td></td>
</tr>
<tr>
<td>B. Absences</td>
<td>1. Typical absences</td>
<td>Absence</td>
</tr>
<tr>
<td></td>
<td>2. Atypical absences</td>
<td>Typical</td>
</tr>
<tr>
<td></td>
<td>3. Myoclonic absences</td>
<td>Myoclonic absences</td>
</tr>
<tr>
<td></td>
<td>C. Myoclonic seizure types</td>
<td>Myoclonic</td>
</tr>
<tr>
<td></td>
<td>1. Myoclonic seizures</td>
<td>Myoclonic</td>
</tr>
<tr>
<td></td>
<td>3. Eyelid myoclonia</td>
<td>Myoclonic tonic</td>
</tr>
<tr>
<td>D. Epileptic spasms</td>
<td></td>
<td>Clonic</td>
</tr>
<tr>
<td>E. Atonic seizures</td>
<td></td>
<td>Atonic</td>
</tr>
<tr>
<td></td>
<td>II. Focal onset (partial)</td>
<td>Focal seizures</td>
</tr>
<tr>
<td>A. Local</td>
<td>1. Neocortical</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>a. Without local spread</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i) Focal clonic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ii) Focal myoclonic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iii) Inhibitory motor seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iv) Focal sensory seizures with elementary symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>v) Aphasic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. With local spread</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i) Jacksonian march seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ii) Focal (asymmetrical) tonic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iii) Focal sensory seizures with experiential symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Hippocampal and parahippocampal</td>
<td></td>
</tr>
<tr>
<td>B. With ipsilateral propagation to</td>
<td>1. Neocortical areas (includes hemiclonic seizures)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Limbic areas (includes gelastic seizures)</td>
<td></td>
</tr>
<tr>
<td>C. With contralateral spread to</td>
<td>1. Neocortical areas (hyperkinetic seizures)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Limbic areas [dyscognitive seizures with or without automatisms (psychomotor)]</td>
<td></td>
</tr>
<tr>
<td>D. Secondarily generalised</td>
<td>1. Tonic–clonic seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Absence seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Epileptic spasms (unverified)</td>
<td></td>
</tr>
<tr>
<td>III. Neonatal seizures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Engel (2006) and Berg et al. (2010).
Table 16.8  The 1989 classification of epilepsies and epileptic syndromes

LOCALISATION-RELATED (FOCAL, LOCAL, PARTIAL) EPILEPSIES AND EPILEPTIC SYNDROMES

Idiopathic (with age-related onset)
- Benign childhood epilepsy with centro-temporal spikes (rolandic epilepsy)
- Childhood epilepsy with occipital paroxysms (Panayiotopoulos type and Gastaut type; early versus later onset with different semiology)
- Primary reading epilepsy

Symptomatic
- Chronic progressive epilepsia partialis continua of childhood (Kojewnikow syndrome)
- Syndromes characterised by seizures with specific modes of precipitation (include focal seizures following acquired lesions, usually involving tactile or proprioceptive stimuli; focal seizures precipitated by sudden arousal or startle epilepsy)
  - Temporal lobe epilepsies;
  - Frontal lobe epilepsies;
  - Parietal lobe epilepsies
  - Occipital lobe epilepsies

Cryptogenic

GENERALISED EPILEPSIES AND SYNDROMES

Idiopathic (with age-related onset)
- Benign neonatal convulsions (isolated or familial)
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (also called in the past 'pyknolepsy')
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal seizures on awakening
- Other generalised epilepsies (not defined above)
- Epilepsies with seizures precipitated by specific modes of activation

Cryptogenic or symptomatic
- West syndrome (infantile spasms, Blitz–Nick–Salaam Krämpfe)
- Lennox–Gastaut syndrome
- Epilepsy with myoclonic–astatic seizures
- Epilepsy with myoclonic absences

Symptomatic
- Early myoclonic encephalopathy
  - Early infantile epileptic encephalopathy with suppression–burst EEG
- Other symptomatic generalised epilepsies not defined above

Specific syndromes (including diseases in which seizures are a presenting or predominant feature)

EPILEPSIES AND EPILEPTIC SYNDROMES UNDETERMINED WHETHER FOCAL OR GENERALISED

With both generalised and focal seizures
- Neonatal seizures
- Severe myoclonic epilepsy in infancy (Dravet syndrome)
- Epilepsy with continuous spike–waves during slow-wave sleep
- Acquired epileptic aphasia (Landau–Kleffner syndrome)
- Other undetermined epilepsies not defined above

Without unequivocal generalised or focal features

Continued
Symptomatic syndromes are those in which seizures are due to the presence of a defined underlying disorder, focal or diffuse; the term cryptogenic includes syndromes that are likely to be secondary to a prenatally-acquired cause but not a primary disorder. Allocation to a particular group may be difficult or impossible, and the definition of the cryptogenic group is unsatisfactory as it depends on the completeness of aetiological investigations.

In 2001, the ILAE Task Force on Classification and Terminology proposed a diagnostic scheme for people with epileptic seizures (Engel 2001). It comprised five axes (Glossary to describe ictal events; List of recognised seizure types; List of epilepsy syndromes, accepting the fact that definitive classification is not always possible; List of diseases often associated with seizures or epilepsy; Impairment resulting from disease). This diagnostic scheme had the advantage of flexibility for use in clinical practice, a factor seriously lacking in previous classifications. However, the terms ‘generalised’, ‘idiopathic’ and ‘symptomatic’ were still included even though they no longer formed the basis for classification. Indeed, although their pathophysiological significance may be limited, the practical value of these terms is difficult to contest.

The ILAE proposal for a revised terminology (Berg et al. 2010) argued that since its first introduction in 1989 the terms idiopathic, symptomatic, and cryptogenic have taken on a variety of meanings and connotations laden with presumptions, which at times, conflate multiple concepts into a single word. It was consequently recommended that the above three terms should be discarded. Instead the following three terms and their associated concepts were recommended:

1. Genetic: The concept of genetic epilepsy implies that epilepsy is best understood as the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom. Knowledge of genetic contributions derive from specific molecular genetic studies that can be replicated and form the basis of diagnostic tests (e.g. SCN1A and Dravet syndrome) or appropriately designed family studies.

2. Structural/metabolic: Structural or metabolic conditions or disease can substantially increase the risk of developing epilepsy. These include acquired disorders such as stroke, trauma, and infection but may also be genetic in origin (e.g. tuberous sclerosis, malformations of cortical development); however, as we currently understand it, there is a separate disorder interposed between the genetic defect and the epilepsy.

3. Unknown cause: Unknown implies that the nature of the underlying cause is unknown; it may have a fundamental genetic defect at its core or be a consequence of a separate, as yet unrecognised, disorder.

The 2010 ILAE proposal also redefined the concept of ‘electroclinical’ syndrome versus disease and introduced novel concepts such as ‘constellations’ on the basis of ‘specific lesions or other causes’ (see Berg et al. 2010).

Although we agree that recent knowledge allows a more precise definition of underlying causes in a small number of the epilepsies, we are not of the opinion that a radical change in terminology will reduce uncertainty for aetiologies (‘known or presumed’ genetic defects) and may increase confusion for non-specialists in epilepsy.

Delineating epilepsy syndromes should permit more precise diagnosis and prognosis than simply classifying seizure types. Epilepsy syndromes are heterogeneous as the link between the components of a particular syndrome may be topographical, aetiological or not understood. More importantly, their specificity is variable. Some syndromes, for example, Rolandic epilepsy, are well defined, whereas others such as grand mal seizures on awakening are linked as a common seizure type. Because the concept of a syndrome is entirely pragmatic and because agreement on the definition is often difficult, only well-defined and generally accepted syndromes are of value (Aicardi 1994; Duchowny and Harvey 1996; Watanabe 1996; Arzimanoglou et al. 2004). Increasing the number of poorly documented subgroups or fitting atypical cases into generally accepted syndromes are two dangers that can defeat the value of the epilepsy syndrome which is to assist in diagnosis, prognosis and management. As a result, a variable proportion of cases of childhood epilepsy are better left unclassified.

In 2016, the ILAE Commission for Classification and Terminology published a special report on new concepts related to the classification of the epilepsies for discussion and debate (Scheffer et al. 2016). The ILAE position paper, published a year later (Scheffer et al. 2017), recognised that as a critical tool for the practicing clinician, epilepsy classification must be relevant and dynamic to changes in thinking, yet robust and
translatable to all areas of the globe. Its primary purpose is for diagnosing patients, but it is also critical for epilepsy research, development of antiepileptic therapies, and communication around the world.

The 2017 ILAE position paper recognised three diagnostic levels, starting with seizure types as defined by their onset characteristics. (also see Fisher et al. 2017a), the next step being diagnosis of epilepsy type. In relation to the data available a patient can be classified as presenting with: focal epilepsy; generalised epilepsy; combined generalised and focal epilepsy; or an unknown type of epilepsy. The third level is that of epilepsy syndrome, if specific syndromic diagnosis is possible.

The new classification also incorporated aetiology in each stage, emphasising the need to consider aetiology at each step of diagnosis, as it often carries significant treatment implications. Aetiology was broken into six subgroups (Structural; Genetic; Infectious; Metabolic; Immune; Unknown), selected because of their potential therapeutic consequences. These categories are non-exclusive as the aetiology may fall into two or more categories (e.g. a structural lesion, result of a genetically determined disorder). Comorbidities should also to be considered.

The framework (Fig. 16.5) elegantly illustrates this multi-level classification, designed to cater to classifying epilepsy in different clinical environments (see also Scheffer et al. 2017).

Current classifications do not account for non-critical manifestations of epilepsy, especially intellectual or psychiatric manifestations. This shortcoming is highly important as epileptic encephalopathy implies that the epileptic activity itself, irrespective of its cause, is responsible for neuropsychiatric manifestations and deterioration. Subclinical epilepsy is purely neurophysiological and generally manifested only by paroxysmal EEG abnormalities. Although a pattern of epileptic encephalopathies is mostly observed in some syndromes such as West syndrome, Lennox–Gastaut syndrome, Dravet syndrome and Electrical Status Epilepticus during Sleep (ESES) occurring in infants and young children, the deleterious role of non-critical manifestations could easily apply to other forms of generalised or focal epilepsy in adults as well as children.

Publication of ‘new’ classifications of epileptic seizures and/or epilepsies undoubtedly reflect evolution of our knowledge in a highly complex field. However, unless strong evidence-based data is utilised to revise existing terminologies, frequent ‘official’ changes in nomenclature increase confusion and produce an opposite effect: general neurologists still refer to ‘epilepsy’ as one entity, perpetuate suboptimal use of diagnostic tools and prescribe antiepileptic drugs (AEDs) rather randomly.
Part VII Paroxysmal Disorders

EPILEPTIC SEIZURES AND EPILEPSY SYNDROMES BY AGE AT ONSET

Age at onset is an important determinant of the prognosis for epileptic disorders and a useful parameter for syndrome diagnosis. This section covers epilepsy syndromes in infancy, early and late childhood and adolescence. Despite broad overlaps, such a division is useful in clinical practice (Table 16.9) for general orientation in diagnosis on the basis of the predominant type of seizures, the choice of the most appropriate investigations and treatment attitudes, and for prognosis (Arzimanoglou et al. 2004, 2016; Duchowny et al. 2013). Because of their specificities reflex epilepsies will be covered in a different section.

In general,

- **the neonatal period** extends from birth to approximately age 3 months in contrast to the conventional interval of the first 4 weeks. During this period, seizures are caused predominantly by structural pathology which carries a poor prognosis. Febrile seizures do not occur during the first 4 months of life; thus, intracranial infection should be diligently searched for in neonates having seizures associated with fever.

- **Infancy and early childhood** (3 months to 4 years) is characterised by either occasional seizures (particularly febrile seizures) or epileptic encephalopathies. Focal epilepsies related to structural lesions may also present with seizures usually occurring during the first 2 years of life.

- **Later childhood and adolescence** is marked either by the onset of idiopathic epilepsies, both focal and generalised of genetic origin or by increased seizure frequency of focal non-idiopathic (structural) epilepsies. Occasional seizures are rare.

SEIZURES AND SYNDROMES OF THE NEONATAL PERIOD

Seizures during the first 28 days of life are a major problem of neonatal neonatal is challenging despite video-EEG analysis that has reduced over-diagnosis of epileptic seizures or their delayed diagnosis and treatment (Arzimanoglou and Aicardi 2001).

NEONATAL SEIZURES

Clinical Features of Neonatal Seizures

The main types of neonatal seizures are shown in Table 16.10. Not all behavioural phenomena classically attributed to neonatal seizures are regularly associated with rhythmic EEG discharges (Mizrahi and Kellaway 1987; Scher and Painter 1990; Mizrahi and Pressler 2015), as seen in older patients. These include clonic seizures, which are always focal with a fixed or shifting location (migratory seizures), and multifocal seizures, which often demonstrate asynchrony between foci that discharge at different rhythms, either simultaneously or in succession. Generalised tonic–clonic seizures are exceptional in this age group; only familial neonatal convulsions are associated with EEG patterns that are also observed at older ages (Hirsch et al. 1993; Ronen et al. 1993). Myoclonic seizures are unusual. Tonic seizures and subtle or 'minimal' seizures that include oral or ocular movements, grimacing, eye opening, blinking or staring, pedalling or boxing movements, and, rarely, isolated apnoea (Watanabe et al. 1982a; Donati et al. 1995) are most common.

A large group of behavioural phenomena, often regarded as seizures on a clinical basis, are not regularly associated with EEG discharges. These include most tonic (generalised or partial) and 'subtle' seizures. Scher et al. (1993a) were able to demonstrate paroxysmal EEG correlates in only 17% of subtle seizures. Such phenomena are often elicited by stimulation; their severity varies with intensity of stimulation, and they may demonstrate temporal or spatial summation (Mizrahi and Kellaway 1987). These patterns may represent 'release' phenomena related to disinhibition of brainstem structures after cortical damage.

The absence of an EEG discharge on the neonatal scalp does not confirm the nonepileptic nature of an event (Volpe 1989; Lombroso 1996) as epileptic seizures without EEG correlates are known to exist. EEG seizure discharges without clinical seizures are also common in neonates (Clancy et al. 1988; Scher and Painter 1990). This is most often noted following repeated seizures treated with anticonvulsants and less frequently, in untreated infants. Brief discharges lasting less than 10 seconds ('brief intermittent rhythmic discharges' or BIRDs) (Scher et al. 1993a, b) are frequent in the newborn EEG and are unassociated with clinical seizure activity. As a result, the definition of neonatal seizures remains imprecise and consequently their incidence is poorly known. Figures quoted vary from 0.15% to 1.4% (Arzimanoglou et al. 2004).

Both term and preterm infants may be affected. Seizures in preterm infants have a more limited expression and subclinical EEG discharges are especially common (Scher et al. 1993a, b; Janáčková et al. 2016).

Neonatal seizures rarely occur as isolated events. Most frequently brief seizures occur repeatedly over a period of a few hours or days (Clancy and Legido 1987; Scher et al. 1993b; Bye and Flanagan 1995) and tend to subside, even without treatment after 24–96 hours. The mean duration of individual seizures is 14.2 minutes for term infants and 3.1 minutes for preterm infants (Scher et al. 1993b), but this difference reflects the frequency of status epilepticus in term infants and its rarity in preterm newborn infants.

Ictal EEG discharges may consist of either focal rhythmic spikes or sharp wave forms at variable frequencies (from alpha to delta) or sharp wave discharges (Tharp 1981; Holmes 1985; Lombroso 1996) in both term and preterm infants (Radvanyi-Bouvet et al. 1985; Legido et al. 1988).
Neonatal seizures should be distinguished from tremors and jitteriness which, although extremely common, are periodic movements. They occur at a rhythm of 5–6 per second, can be suppressed by restraint or repositioning (Kramer and Harel 1994; Fernández-Alvarez and Aicardi 2001) and have a favourable outcome. Seizures should also be distinguished from benign neonatal sleep myoclonus (Chapter 21); and vegetative phenomena such as nonepileptic apnoea. It is especially challenging to diagnose atypical seizures with suggestive clinical manifestations that are unassociated with EEG paroxysms as epileptic in origin. The problem is often unresolved, making a decision on treatment difficult (Hellström-Westas 2015).

Clinical recognition of nonepileptic phenomena in neonates is often possible. Important diagnostic clues include the ability to elicit abnormal phenomena by stimulation, whether tactile or otherwise; the demonstration that temporal or spatial summation of stimuli is effective; and the ability to prevent or interrupt abnormal events by restraint. More importantly, the clinician must consider the neurological context within which the paroxysmal phenomena are observed (Arzimanoglou and Aicardi 2001).

### Aetiology of Neonatal Seizures

The main causes of neonatal seizures are listed in Table 16.11. Many seizures associated with intracranial haemorrhage or inborn errors of metabolism are probably not epileptic; the same applies to hypoxic–ischaemic encephalopathy (HIE), despite being a common cause of neonatal seizures (Levene and Trounce 1986; Vasudevan and Levene 2013). Many infants with HIE have already been injured in utero, as shown by the frequency of prenatal placental damage (Burke and Tannenberg 1995; Scher 2003). Perinatal events may therefore not be significant. Seizures after HIE typically occur within the first 24–48 hours of life, and are regularly associated with other symptoms including behavioural suppression or coma (Chapter 1). The EEG in severe cases is typically severely attenuated or discontinuous (‘tracé paroxystique’).

Localised arterial infarction is an important cause of localised, fixed clonic seizures (Levy et al. 1985). Scher et al. (1993a) noted infarctions in 58% of their cases of EEG-confirmed neonatal seizures.

Infections are mainly of viral origin. However, the frequency of meningitis and encephalitis is sufficiently high to justify lumbar puncture whenever there is no other obvious cause.

Hypocalcaemia and hypoglycaemia (Cornblath and Schwartz 1991) are much less common but treatable conditions. Late hypocalcaemia due to high phosphorus load in artificial milk feeds is now rarely seen, and currently observed cases are often associated with cardiac disease and have a guarded prognosis (Lynch and Rust 1994). Early hypocalcaemia is usually associated with other problems, so other causes for the seizures should be sought in affected patients. De Vivo et al. (1991) described a defect of glucose transport across the blood–brain barrier caused by the genetic absence of the GLUT1 protein causing severe hypoglycorrhachia accompanied by isolated seizures without hypoglycaemia. Onset usually occurs toward the end of the first month of life but neonatal and late onset can occur (see also Chapters 9 and 16).

Rare metabolic causes include pyridoxine dependency (see also Chapters 9 and 27), spongiform encephalopathy with low activity of Na/K pumps (Renkawek et al. 1992), pyridoxal-dependent seizures and familial folinic acid-responsive seizures (Hyland et al. 1995; Baxter 2002; Wolf et al. 2005; Campistol and Plecko 2015). Cases of neonatal seizures resistant to pyridoxine but responsive to pyridoxal phosphate have been reported (Wang et al. 2005).
Epileptic seizures related to hereditary metabolic disorders are usually associated with widespread neurological dysfunction. A key diagnostic feature is the early appearance of symptoms, following a symptom-free period of a few hours or days, particularly if otherwise unexplained (no antenatal or prenatal history). The diversity of causes calls for rigorous analysis of symptoms and of biological samples in the interest of rapid diagnosis and the most appropriate treatment (Livet et al. 2005; Campistol and Plecko 2015). Seizure types and EEG patterns are rarely specific for any particular metabolic disorder (Wolf et al. 2005).

### Table 16.10  Features of the main types of neonatal seizures

<table>
<thead>
<tr>
<th>Type of seizures</th>
<th>Clinical features</th>
<th>Ictal paroxysmal EEG discharges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised tonic–clonic</td>
<td>Tonic contraction followed by a few jerks. Seen only with benign familial neonatal convulsions</td>
<td>Present in most cases</td>
</tr>
<tr>
<td>Generalised tonic</td>
<td>Sustained symmetrical posturing of neck and trunk sometimes provoked by stimulation</td>
<td>Rarely present</td>
</tr>
<tr>
<td>Focal clonic</td>
<td>Rhythrical jerks, focal or multifocal (in this case often asynchronous) Not suppressed by restraint</td>
<td>Almost always present</td>
</tr>
<tr>
<td>Focal tonic</td>
<td>Sustained posturing of single limb, sustained eye deviation not suppressed by restraint</td>
<td>Present in some cases</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Arrhythmical, nonrepetitive jerks, generalised, focal or fragmentary</td>
<td>Present in 80% of cases</td>
</tr>
<tr>
<td>Subtle or minimal seizures or motor automatisms</td>
<td>Roving eye movements, blinking, grimacing, sucking, chewing, thrusting tongue movements, swimming, boxing or cycling movements, suppressed by restraint and precipitated by stimulation when nonepileptic</td>
<td>Seldom present</td>
</tr>
</tbody>
</table>

### Table 16.11  Main causes of neonatal seizures

**Hypoxic–ischaemic encephalopathy**

(may produce both clearly epileptic seizures and seizures probably nonepileptic in nature)

**Intracranial haemorrhage**

Subarachnoid haemorrhage (clonic seizures in term infants 1–5 days of age)

Intraventricular haemorrhage (mainly tonic seizures and episodes of apnoea without EEG correlates, occasionally typical EEG discharges)

Intracerebral haematoma (fixed localised clonic seizures)

**Intracranial infections**

Bacterial meningitis and/or abscess

Viral meningoencephalitis

**Cerebral malformations**

Myoclonic and focal tonic seizures, infantile epileptic spasms, others

**Metabolic causes**

Hypocalcaemia (clonic, multifocal seizures)

Hypoglycaemia

Hyponatraemia

Inborn errors of amino acids or organic acids and NH3 metabolism (often atypical, mostly unassociated with EEG discharges)

Molybdenum cofactor deficiency

Bilirubin encephalopathy (atypical, no EEG discharges)

Pyridoxine dependency

Biotinidase deficiency

Carbohydrate-deficient glycoprotein syndrome

**Toxic or withdrawal seizures** (probably not true epileptic seizures in most cases)

**Familial neonatal convulsions** (clonic localised, shifting seizures with EEG correlates)

‘Benign’ neonatal seizures of unknown origin (‘fifth-day fits’)

Clonic and apnoeic seizures with typical EEG correlates
Seizures in infants born to mothers addicted to narcotics or barbiturates are typically nonepileptic in origin but EEGs have only rarely been recorded in such cases. Their prognosis appears to be favourable (Doberczak et al. 1988).

Seizures due to cerebral malformations include infantile spasms and myoclonic patterns. Neonatal convulsions without detectable cause are not uncommon (Painter et al. 1986; Aicardi 1991).

The aetiologic profile and neurodevelopmental outcome of seizures in term newborn infants was studied by Telgul et al. (2006). Eighty-nine term infants with clinical neonatal seizures were evaluated in the newborn period and at 12–18 months. Aetiology was defined in 77 infants. Global cerebral hypoxia–ischaemia, focal cerebral hypoxia–ischaemia, and intracranial haemorrhage were most common. Neonatal mortality was 7%, and 28% of survivors had poor long-term outcome. Association between seizure aetiology and poor outcome was strong, with cerebral dysgenesis and global hypoxia–ischaemia associated with the poorest outcome. A normal neonatal period/early infancy neurological examination was associated with uniformly favourable outcomes at 12–18 months; neurological abnormalities lacked specificity. A normal or mildly abnormal neonatal EEG had a favourable outcome, particularly if neonatal neuroimaging was normal. A moderate or severely abnormal EEG and multifocal and diffuse cortical or primary deep grey matter lesions carried a poorer prognosis. Mortality associated with neonatal seizures has declined in the current era of neonatal intensive care, although long-term neurodevelopmental morbidity remains unchanged. Seizure aetiology and background EEG patterns are important prognostic factors.

Neuroimaging is very helpful to identify the underlying aetiology. Cranial ultrasound is more suitable for identifying severe and centrally located lesions during the acute phase; calcifications can also be identified by ultrasound and are typically unrecognised on MRI. More detailed information will subsequently be obtained with MRI, using thin (2mm) slices and sequences suitable for imaging neonates. MRI is especially useful in revealing migrational disorders. Magnetic resonance spectroscopy may be used to identify metabolic disorders before the results of metabolic investigations are available (Wecke et al. 2015; Campistol and Plecko 2015).

**SYNDROMES OF THE NEONATAL AND EARLY INFANTESTILE PERIOD**

Only a few well-defined syndromes are currently recognised in newborn infants.

**Benign Familial Neonatal Seizures (BFNS)**

Benign familial neonatal seizures (BFNS) are dominantly inherited. The most frequently implicated gene is located on chromosome 20q (Leppert et al. 1989; Malafosse et al. 1994) and codes for the KCNQ2 potassium channel (Singh et al. 1992), but rare cases are linked to chromosome 8 on a gene for KCNQ3 (Ryan et al. 1991; Charlier et al. 1998). In other cases, no linkage to either locus has been found (Plouin 1994).

Seizure onset occurs within 2–15 days of birth, recur for a few days, then cease. Later relapses occur in 14% of cases (for a review see Plouin and Neubauer 2012). Seizures are generalised (Hirsch et al. 1993; Ronen et al. 1993), although focal seizures have been reported (Aso and Watanabe 1992; Bye 1994). The phenotype is variable with some members of affected families presenting with febrile convulsions or generalised epilepsies (Berkovic et al. 1994). Rare cases of apparent recessively inherited neonatal seizures have been reported (Schiffmann et al. 1991). Diagnosis rests on a history of similar events in relatives, consistent with an autosomal dominant transmission. A mutation of the SCNA2 sodium channel subunit has been found in a subtype in which seizure onset may be either neonatal or infantile (see below). The phenotypic, functional and mutational variations in BFNC are reviewed in a study of 17 families with KCNQ2 mutations (Singh et al. 2003).

The natural course of the seizures is self-limited, as seizures cease within a few days or weeks. In two members of one family, the phenotype extended beyond neonatal seizures and included rolandic seizures, while a subset of families experienced seizure in infancy. One patient with BFNS that evolved to rolandic epilepsy was reported by Coppola et al. (2003). Ten to 15% of patients have febrile or afebrile seizures later in life (Ronen et al. 1993) while showing normal psychomotor development. There are no published guidelines for treating benign familial neonatal convulsions. Formerly no treatment was offered (Plouin and Anderson 2005). Phenobarbitone, sodium valproate or phenytoin are the classic drugs of choice and are administered over a period of 3–6 months. Data on long-term more recent AEDs, such as levetiracetam and topiramate are not yet available (Ikonomidou 2015).

**Benign Familial Infantile Convulsions (BFIC)**

A slightly later seizure onset was observed in several families and named benign familial infantile convulsions (BFIC). Their presentation is characterised by focal seizures, with or without secondary generalisation, occurring mostly in clusters, and with onset between ages 3–9 months. Patients typically have normal psychomotor development at seizure onset and a favourable outcome (Vigevano et al. 1992; Chahine and Mikati 2006). The condition is genetically heterogeneous with loci identified on chromosomes 19q12–13.1 and 16p12–q12, allelic to infantile convulsions and choreoathetosis. Mutations were subsequently identified in the gene encoding the voltage-gated sodium channel a2 subunit (SCN24) on chromosome 2q24 (Heron et al. 2002) in two families affected by neonatal and infantile seizures (benign familial neonatal–infantile convulsions) and confirmed in six other families investigated by the same group (Berkovic et al. 2004).
The relevance of chromosome 16 locus in BFIC was confirmed in a recent study of 16 families (Striano et al. 2006).

**Benign non-familial neonatal convulsions** (Plouin and Neubauer 2012), also known as ‘fifth day seizures’, consist of repeated seizures mainly clonic or apnoeic in type with onset between 3 and 7 days of age. The interictal neurological state and EEG are normal, although the latter may show peaked theta rhythm (so-called théta pointu antœratun) (Plouin 1994). Neonatal seizures of late onset (after 3 days) without known cause often have a favourable outcome (Lombroso 1996).

**KCNQ2 Encephalopathy**

**KCNQ2 encephalopathy** is a recently described entity, characterised by drug-resistant seizures of neonatal onset and severe psychomotor impairment (Weckhuysen et al. 2012, 2013). Age at onset is nearly identical to BFNS, (first week of life), and the seizure pattern is also similar – a prominent tonic component with or without associated clonic jerking of the face or limbs. Motor manifestations are often associated with autonomic features such as apnoea and desaturation (Serino et al. 2013). Further evolution is distinct from BFNS as seizure frequency increases dramatically, sometimes up to 10 per hour. All affected children have a severely abnormal interictal EEG pattern, either burst suppression or multifocal epileptic activity. Treatment is usually ineffective at symptom onset. While many children achieve seizure-freedom by the first or second year of life, their psychomotor development remains profoundly impaired. A recent report (Numis et al. 2014) described three cases with dramatic seizure control following the introduction of oral carbamazepine but psychomotor development was still impaired (for a discussion on mechanisms probably involved, refer to the review by Cilio and Oldham 2015).

**Epileptic Encephalopathy Associated with CDKL5 Mutations**

**Epileptic encephalopathy associated with CDKL5 mutations**, first described in 2003 (Kalscheuer et al. 2003), is another well-delineated entity with the majority of the patients having onset of seizures within the first 3 months of life (Bahi-Buisson et al. 2008). A three-phase course is reported starting with frequent, albeit brief seizures, hypotonia and poor eye contact. Even with proper seizure management, the second phase progresses to epileptic spasms, with or without hypsarrhythmia that evolves into a severe epilepsy with multiple seizure types, including myoclonic and tonic. A distinctive seizure pattern, described as ‘hypermotor-tonic-spasms’ may appear during the first or the second stage (Klein et al. 2011). Because the syndrome is more frequently seen in girls accompanied by deceleration of head growth and hand stereotypes, a Rett-variant has been proposed. However, this hypothesis is not supported by a recent excellent review (Fehr et al. 2013) based on a large international cohort including over 80 children (77 females and nine males).

**Syndrome of Focal Neonatal Convulsions and Stroke**

The **syndrome of focal neonatal convulsions and stroke** is less well defined. However, this diagnosis should be considered by the occurrence in the 2nd to 7th day of age of repeated focal clonic seizures that remain localised to the same restricted part of the body. The diagnosis is confirmed by neuroimaging revealing the presence of infarction involving mostly the middle cerebral artery territory. The overall prognosis is favourable but hemiplegia persists in about half the cases. Some patients develop later focal or unilateral ESES and present with learning difficulties.

Severe neonatal or infantile epilepsies with suppression-burst pattern (early infantile epileptic encephalopathy with suppression–bursts or Ohtahara syndrome and early neonatal myoclonic encephalopathy) are discussed in the Seizures and Syndromes of Infancy and Early Childhood section.

Prenatal seizures have been demonstrated by ultrasonography (Landy et al. 1989; Du Plessis et al. 1993). They may occur with pyridoxine dependency and with some brain malformations (Du Plessis et al. 1993).

**Prognosis in Neonatal Seizures**

The prognosis in neonatal seizures is mainly determined by their cause (Volpe 1989; Lombroso 1996; Tegkul et al. 2006). The possible role of the seizures themselves in generating or increasing brain damage remains controversial (Volpe 1989; Lombroso 1996; Scher 2003). Although some aggravating effect of seizures is likely, the occurrence of seizures of long duration without sequelae, such as those of hypocalcaemia or of familial seizures, suggests that the role of paroxysmal activity (Lombroso 1996) is less important than its causes.

The poorest outcome occurs in patients with seizures due to brain dysplasias (an often surgically treatable aetiology particularly when identified early), followed by hypoxic–ischaemic encephalopathy and neonatal infections. These disorders carry a high mortality and have a high incidence of later epilepsy, intellectual disability and cerebral palsy (Holden et al. 1982; Watanabe et al. 1982b; Lombroso 1983b, 1996). In contrast, the prognosis for some metabolic seizures (late hypocalcaemia) and seizures of unknown cause with onset after the second day of life is largely favourable (Arzimanoglou and Aicardi 2001). In a series of patients with electroencephalographically confirmed seizures, the mortality was 32.5% and sequelae were found in 55.5% of survivors (Legido et al. 1988). Late epilepsy occurs in 10–26% of patients but may be as high as 81% in patients with large brain malformation.

The prognostic value of the interictal EEG for neurodevelopment has been repeatedly emphasised (Lombroso 1983b; Scher and Beggarly 1989). Long-term prognosis was also studied in a prospective population-based study of 88 participants (Ronen et al. 2007). Prognosis was better for term than preterm infants (P=0.003). The authors reported for term infants: 28 (45%) normal, 10 (16%) deaths and 24 (39%) with impairments; in comparison, preterm infants...
showed: three (12%) normal, 11 (42%) deaths and 12 (46%) with impairments. Of survivors, 17 (27%) developed epilepsy, 16 (25%) had cerebral palsy, 13 (20%) had intellectual disability and 17 (27%) had learning disorders. Variables associated with poor prognosis were Sarnat stage III or equivalent severe encephalopathy, cerebral dysgenesis, complicated intraventricular haemorrhage, infections in preterm infants, abnormal neonatal EEGs, and the need for multiple drugs to treat neonatal seizures. Pure clonic seizures without facial involvement in term infants were associated with a favourable outcome, whereas generalised myoclonic seizures in preterm infants were associated with high mortality.

**Treatment of Neonatal Seizures**

Symptomatic treatment is imperative in addition to treatment of the cause of seizures. This includes maintaining a clear airway and vital signs (cardiac rate, blood pressure, etc.) and administering specific therapy (e.g. late hypocaelemia, hypomagnesaemia and some cases of hypoglycaemia). Pyridoxine and pyridoxal phosphate should be administered. A single dose of 100mg of pyridoxine for all neonates is standard; excessive doses should be avoided as hypotonia and apnoea may result (Kroll 1985).

As a direct result of lack of controlled trials in neonates, antiepileptic drug treatment still commonly relies on phenobarbitone or phenytoin, but these are only 50% effective (Booth and Evans 2004; Pressler and Mangum 2013). Large loading doses are usually recommended (phenytoin, a single intravenous dose of 20mg/kg, not to be repeated – further doses can be administered while monitoring serum levels; phenobarbitone, 20–25mg/kg/day – some authors use doses as high as 30–120mg/kg/day in 10mg/kg boluses every 30 minutes), provided ventilatory support is available (Crawford et al. 1988). However, anticonvulsant agents may have deleterious effects on the neonatal brain (Mikati et al. 1994) and their efficacy is not established. Painter et al. (1999) found similar efficacy between phenobarbitone and phenytoin. More importantly, seizure frequency decreased if a decreasing trend had occurred previously, and the drugs failed to prevent subsequent seizures, to delay seizure recurrence or attenuate the severity. Furthermore, antiepileptic agents may eliminate clinical seizure expression without modifying the ictal EEG.

Benzodiazepines, especially lorazepam, is often a first-line or single therapy (Lombroso 1983b; Deshmukh et al. 1986; Hakeem and Wallace 1990). A retrospective non-randomised study (Castro Conde et al. 2005) demonstrated complete electrical control with midazolam in 13 phenobarbitone and phenytoin non-responders and encountered no adverse reactions.

We have found that the use of benzodiazepines as first-line agents often obviates the need for additional therapies. Lidocaine and paraldehyde administration are rarely utilised. Maintenance treatment should be carefully monitored as most AEDs are slowly metabolised in the neonatal period creating a risk of accumulation. In fact, prolonged treatment of neonatal seizures is probably not warranted except for major structural brain abnormalities, as neonatal seizures have a strong tendency to be short-lasting (Hellström-Westas et al. 1995).

The treatment of neonatal seizures remains challenging (Sankar and Painter 2005; Ikonomidou 2015). The two most commonly used medications, phenobarbitone and phenytoin were introduced as anticonvulsants in 1912 and 1938 for adult seizures; they were only secondarily employed in infants and children. Little is known about their effects on cellular and network excitability or early brain development. The choice of phenobarbitone or phenytoin (currently formulated as fosphenytoin) largely rests on their availability in parenteral dosage forms for preterm infants and the relative comfort level of treating physicians (Sankar and Painter 2005). Data are scarce concerning newer AEDs.

A Cochrane review of randomised controlled trials (Booth and Evans 2004) revealed little evidence to support the use of any of current anticonvulsants in the neonatal period. A similar conclusion was confirmed in a more recent systematic review of existing literature (Slaughter et al. 2013). The 2007 Cochrane review (Evans et al. 2007), focusing more specifically on perinatal asphyxia-related seizures, also underscored that anticonvulsant therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures.

There remains a body of opinion that seizures should be treated because of the concern that seizures in themselves may be harmful, although this is only supported by relatively low-grade evidence. Development of safe and effective treatment strategies relies on future studies of high quality (randomised controlled trials with methodology that assures validity) and of sufficient size to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability in addition to any short-term reduction in seizure burden (see also Pressler and Mangum 2013).

As for emerging therapies for neonatal seizures, preclinical data suggested that the loop-diuretic bumetanide could be an effective treatment for neonatal seizures. However, the NEMO study (Pressler et al. 2015), evaluating bumetanide as an add-on to phenobarbital, did not confirm this hypothesis in newborn infants with hypoxic–ischaemic encephalopathy. They also found that bumetanide might increase the risk of hearing loss, highlighting the risks associated with the off-label use of drugs in newborn infants before safety assessment in controlled trials.

There are encouraging developments, both in terms of the use of newer AEDs (Ikonomidou 2015; Arzimanoglou et al. 2016c) and hypothermia (Low et al. 2012; Srinivasakumar et al. 2013) to improve antiepileptic efficacy as well as novel measures to prevent neurotoxicity. Lithium and melatonin are promising agents (Ikonomidou 2015).

In 2011, with the contribution of the ILAE, the World Health Organization (2011) published *Guidelines on Neonatal Seizures*, an evidence-based document which provides diagnostic and management recommendations which can be used in different health care settings.
Almost all forms of epilepsy may begin in this age range (Elze 2015), including focal epilepsies (to be discussed in the Seizures and Syndromes of Late Childhood and Adolescence section), rare forms of idiopathic epilepsies such as myoclonic epilepsy of infancy and, particularly, the so-called epileptic encephalopathies (West syndrome, Dravet syndrome, Lennox–Gastaut syndrome). Epilepsies with predominantly myoclonic–astatic seizures may also begin at this age range (Arzimanoglou and Resnick 2011).

In infants and young children under 2–3 years, behavioural problems predominate even more than seizures, and deterioration, whether cognitive or behavioural or both, may occur. The term ‘epileptic encephalopathy’ is often used to characterise this phenomenon, presuming that the epilepsy itself contributes significantly to global deterioration.

Finally, this period is remarkable because of the high susceptibility of the CNS to several extrinsic changes, particularly fever, leading to frequent occurrence of occasional seizures. Although febrile seizures, because of their transient nature, are not a form of epilepsy in the classic sense of the term, they are included at the end of this section as they pose a number of important related diagnostic and therapeutic issues.

**Infantile Epileptic Spasms (including West Syndrome)**

The classic syndrome, known as Infantile Spasms or West syndrome, has three major components: infantile epileptic spasms, interictal EEG tracing of hypsarrhythmia that accompanies the seizures in a typical or modified form, and the presence of cognitive and behavioural regression (Lux and Osborne 2004; Guzzetta et al. 2007). One of the elements of the triad may be absent (commonly the hypsarrhythmia), and additional features such as focal seizures, marked asymmetries and focal neurological signs may be associated (Arzimanoglou et al. 2004; Dulac and Tuxhorn 2005; Guzzetta et al. 2007). The incidence of West syndrome is estimated at 3–4.5 per 10,000 live births. The term West syndrome should probably be reserved only for cases presenting both epileptic infantile spasms, a chaotic interictal EEG pattern (see below) and signs of developmental regression (that at onset can be limited to a loss of some acquired skills).

West syndrome virtually always begins during the first year of life, with a peak frequency between 4 and 10 months of age; more rarely epileptic spasms begin shortly after birth. Epileptic spasms can also occur outside the infantile period and may account for epileptic falls or head drops (Egli et al. 1985; Ikeno et al. 1985; Auvin et al. 2010).

Infantile epileptic spasms are the characteristic and often sole type of seizures in West syndrome but may be preceded, accompanied or followed by other types of seizures. The spasms are sudden, usually bilateral, tonic contractions of the muscles of the neck, trunk and extremities that may be flexor or extensor. The intense abrupt contraction lasts less than 2 seconds but may be followed by a less intense contraction with or without behavioural arrest lasting about 10 seconds. The spasms are sometimes isolated but characteristically occur in a series up to more than 100 individual jerks, 5–30 seconds apart. The repetitive character of the spasms is an important diagnostic clue, especially as the individual spasms may have a very limited expression such as slight head nodding, elevation of the eyeballs or shrugging of the shoulders, which are all too often discounted as colic, Moro reflex or other benign phenomena.

Clinical variants, especially unilateral spasms, are relatively common (Shewmon 1994; Gaily et al. 1995). Asymmetrical and even unilateral spasms may occur and are usually associated with contralateral EEG activity, suggesting a cortical generator for infantile spasms (Donat and Wright 1991a, c; Gaily et al. 1995), and with damage to the same side. Abnormal cortical development is one of the most frequently encountered causes of asymmetrical infantile spasms (Metsähonkala et al. 2015). Early identification of the responsible focal lesion is of major importance when deciding the most appropriate therapeutic strategy as focal dysplastic lesions are often surgically amenable. Other types of seizures may precede or accompany the spasms.
Chapter 16 Epilepsy and Other Seizure Disorders

The ictal EEG features of epileptic spasms usually consist of a generalised high-amplitude slow wave coinciding with the clinical event, often with superimposed fast activity (Vigevano et al. 2001). The latter may appear in isolation (Donat and Wright 1991c; Shewmon 1994). Other patterns have been reported but appear to be rare.

Hypsarrhythmia (Fig. 16.6) is the most characteristic interictal EEG pattern associated with West syndrome. It is characterised by a chaotic succession of very high-amplitude slow waves interspersed at random with multifocal asynchronous spikes and sharp waves. During slow sleep, bursts of polyspikes separated by stretches of poorly active tracings are typically present (Vigevano et al. 2001; Dulac and Tuxhorn 2005). Because hypsarrhythmia may induce cognitive and behavioural dysfunction, certain authors (Dalla Bernardina et al. 2007) suggest that it cannot be considered strictly an ‘interictal’ pattern, the entire electroclinical picture representing a continuous ictal status modified by the recurrence of more or less easily detectable ‘ictal events’.

Modified hypsarrhythmia, with preservation of some background rhythms, localising features or synchronous spike–wave activity occurs in up to 40–70% of cases. Unilateral hypsarrhythmia is rare, usually associated with unilateral spasms (Gaily et al. 1995). Several other EEG patterns can be associated with infantile spasms, and only 60% of patients were reported to have true or modified hypsarrhythmia (Dalla Bernardina and Watanabe 1994). Some infants may have nonparoxysmal EEG for a brief period at onset of the disorder or late in the course, despite persistence of the clinical spasms.

Focal EEG features may be present together with the hypsarrhythmia as foci of spikes or as localised slow waves especially during sleep. They are of value as they indicate the likelihood of a cortical lesion, thus favouring a structural cause.

Developmental deficits are present before the onset of the spasms in 68–85% of cases (Riikonen 1982). Such figures are minimal estimates as mild degrees of cognitive delay are difficult to identify at an early age. In infants who were previously well, a definite behavioural regression is observed (Guzzetta et al. 2002), the infants losing interest in their surroundings sometimes to the point of appearing blind and deaf, or simply limited to loss of previously acquired skills, usually obvious to the parents. Deterioration may seem to be the first manifestation of the syndrome when the spasms are delayed or escape recognition, and West syndrome should be considered in any infant who regresses developmentally during the first year of life. Development usually improves when the seizures subside although resumption of cognitive functioning may lag for several weeks after cessation of seizures.

Autistic features are common at the onset of West syndrome and may persist as a sequela in a high proportion of patients (Riikonen and Amnell 1981). Guzzetta et al. (1993) have clearly separated the manifestations of the acute phase, comprising mainly disturbances of awareness and communication, from the cognitive sequelae.

The diagnosis of infantile epileptic spasms should be straightforward if the repetitive character of the spasms and the associated phenomena are given due attention. However, only 12% of primary care physicians made the correct diagnosis in one series (Bellman et al. 1983), whereas 15% made a diagnosis of colic. Benign myoclonus of infancy is an axial shudder that may closely mimic infantile spasms but the EEG is normal (Lombroso and Fejerman 1977; Pachatz et al. 1999). This nonepileptic phenomenon seems related to tics or ‘gratification phenomena’. Other forms of epilepsy, especially myoclonic epilepsies (either idiopathic or of an unknown cause), are also erroneously diagnosed as infantile spasms, although their prognosis is more favourable. Early-onset Lennox–Gastaut syndrome may be difficult to differentiate as

Figure 16.6 Hypsarrhythmia in a child with epileptic infantile spasms. Sleep EEG showing high amplitude disorganised background activity with multifocal irregular spikes and waves and absence of normal sleep EEG patterns. (Courtesy Dept of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon, France.)

(Lombroso 1983a; Donat and Wright 1991b; Carrazana et al. 1993; Plouin and Dulac 1994).

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seizures can occur in clusters in both syndromes (Donat and Wright 1991a).

Prognosis of infantile spasms depends primarily on aetiology. For this reason, a detailed diagnostic workup, with priorities decided on the basis of the overall clinical and EEG picture, should be considered an absolute priority at onset and entrusted to a child neurology team specialised in epilepsy.

An important distinction is made between symptomatic and cryptogenic spasms. Cryptogenic cases are variably defined as those for which no cause can be identified or those that, in addition, showed normal development before the onset of seizures (Lombroso 1983a). The term cryptogenic does not exclude the presence of a lesion, thus blurring the distinction between the two categories. With the latter definition, cryptogenic spasms account for only 10–15% of cases, but these are much more likely than symptomatic (structural/metabolic) cases to run a favourable course.

Some investigators (Vigevano et al. 1993; Dulac and Tuxhorn 2005) described an idiopathic group of infantile spasms with a good prognosis and peculiar clinical and EEG features. However, Haga et al. (1995) and Watanabe et al. (2001) were unable to differentiate aetiological groups on the sole basis of clinical or EEG (ictal or inter-ictal) features. Structural causes are most commonly due to brain malformations and neocutaneous syndromes (mainly tuberous sclerosis) (Vigevano et al. 1994a; Arzimanoglou et al. 2004; Dulac and Tuxhorn 2005). Gross malformations include lissencephaly, pachygyria, diffuse subcortical heterotopias and agenesis of the corpus callosum, especially Aicardi syndrome (see Chapter 1). Tuberous sclerosis accounts for 10–20% of cases. Focal cortical malformations also account for the majority of remaining symptomatic cases (Cowen and Hudson 1991). Metabolic diseases are uncommonly causative. Infantile spasms are also observed in chromosomal disorders (see Chapter 5) associated with epilepsy (Battaglia and Guerrini 2005).

West syndrome is usually sporadic, except when due to metabolic disorders. Genetically determined forms are uncommon. X-linked cases are mainly due to mutations in the ARX gene (Suri 2005) and may be associated with other abnormalities, some of which are congenital. Other cases due to mutations at chromosome Xp11p11–Xpter (Claes et al. 1997) and in the CDLKS gene (Weaving et al. 2004; Bahl-Buisson et al. 2008) have been reported. Spasms are also a feature of the PEHO syndrome (peripheral oedema, hypsarhythmia and optic atrophy) (Chapter 10). From a pathological standpoint, most autosomal cases of infantile spasms are due to prenatal factors. Meencke and Gerhard (1985) found no detectable pathology in only 11% of 107 cases. Most cases are related to diffuse lesions, but unilateral lesions, in particular cystic encephalomalacia in the middle artery territory (porencephalic cysts) (Palm et al. 1988), may be responsible for infantile spasms with a more favourable prognosis (Alvarez et al. 1987; Cusmai et al. 1988).

Treatment of West syndrome is often unsatisfactory and the response highly related to the underlying aetiology. Most conventional AEDs are ineffective. So far, only corticosteroids or adrenocorticotropic hormone (ACTH) and vigabatrin are recognised as effective (see Hancock et al. 2013) and the American Academy of Neurology Practice parameters (Mackay et al. 2004). According to a Cochrane analysis (Hancock et al. 2013), there are few well-designed randomised controlled trials of treatment for infantile spasms, and the number of patients enrolled has been small. In the majority, methodology has been poor. Hormonal treatment resolves spasms in more infants than vigabatrin, but this may or may not translate into better long-term outcomes. High dosage is recommended if prednisolone or vigabatrin is used. Vigabatrin is considered the treatment of choice in patients with tuberous sclerosis complex. Resolution of EEG features may be important, but this has not been proven. Other agents, for example, topiramate, lamotrigine, valproate, pyridoxine and zonisamide, and non-pharmacological methods have been found useful by some authors (for reviews see Dulac and Tuxhorn 2005; Hancock et al. 2013).

All reports conclude on the need for well-designed, prospective studies with larger numbers of participants and a long follow-up. However, the authors of the present chapter believe that 174 years from the first description of the syndrome by James West and 57 years after the first prescription of ACTH to children with epileptic spasms, lack of controlled studies may be due to various reasons. This includes the use of studies utilising methodologies applied to other syndromes that are not applicable to epileptic spasms. The lack of a suitable animal experimental model of infantile spasms is also limiting. Lastly, the high risk of permanent cognitive impairment from an encephalopathic disorder is problematic for a placebo-controlled trial. We suggest that future studies should be limited to specific aetiologies, as, for example, early surgery versus ACTH or vigabatrin in infants with dysplasias, tuberous sclerosis, metabolic diseases, and so on.

**HORMONAL TREATMENT AND VIGABATRIN TREATMENT**

ACTH and corticosteroids are both in widespread clinical use. The spectrum of ACTH therapy is extremely variable. ACTH doses vary from 10 to 40 units of natural hormone or 0.1–0.5mg/kg as tetracosactide. Corticosteroids including prednisolone at 2–10mg/kg, hydrocortisone at 5–20mg/kg/day and dexamethasone at 0.3–0.5mg/kg/day are used alone or in various combinations with ACTH. Only a few controlled studies and even fewer comparative studies have been performed (Glaze et al. 1988; Mackay et al. 2004).

One controlled comparative study of tetracosactide versus prednisolone found ACTH to be more effective in a small number of patients, producing remission in 13 of 15 infants compared to four of 14 receiving prednisolone (Baram et al. 1996). In contrast, the large controlled United Kingdom Infantile Spasms Study (UKISS; Lux et al. 2005) did not demonstrate any superiority of one agent over the other. High-dose ACTH (150IU/kg/day) was not found more effective than low-dose.
ACTH (20IU/kg/day) in another study (Hrachovy et al. 1994), and two low-dose regimes of tetracosactide showed no difference between the lower and higher dosages (Kondo et al. 2005). Various other protocols are currently available. Heiskala et al. (1996) proposed individualising progressive ACTH therapy, starting with a dose of 3IU/kg/day and progressively increasing to a maximum of 12IU/kg/day if no response is obtained. The clinical impression is that some cases may respond selectively to either agent.

Corticosteroids obviate the need for injection and shorten hospitalisation, and many clinicians continue their use for this reason. However, ACTH might be preferred if its superiority were confirmed in more convincing, larger studies. The mode of action of both agents is unknown. Duration of treatment is no less variable, from 3 to 4 weeks to several months. Our own practice is to use hormonal treatment for short periods of the order of 4–6 weeks.

ACTH or steroid therapy controls spasms in 50–70% of cases but normalise or improve the EEG in a slightly lower proportion. Relapses occur in 20–35% of patients. The long-term neurodevelopmental benefit of therapy is less striking (Riikonen 1996; Gaily et al. 1999; Goh et al. 2005), with normal cognitive development in about 25–30% and only mild impairment in an additional 10–15%. The outcome is better in cryptogenic cases where the proportions are respectively 50% and 25%. Seizures persist in approximately half the patients. They commonly present with the characteristics of the Lennox–Gastaut syndrome, but focal seizures are also observed.

Side effects of ACTH or corticosteroids are common and are often severe if higher doses are administered for longer terms. These include hypertension, infections and metabolic disturbances. Brain shrinkage may also be observed (Konishi et al. 1992). Neuroimaging assessment of patients is therefore best performed before starting treatment.

Vigabatrin has been shown to be efficacious in several studies (for reviews see Arzimanoglou et al. 2004; Dulac and Tuxhorn 2005; Hancock et al. 2013). Doses of 100–150mg/day control spasms in approximately 50–60% of cases usually in less than a week. Its effect on EEG abnormalities is slower than for corticosteroids. In a comparative study with hormonal treatment as first-line therapy (Vigevano and Cilio 1997), vigabatrin was more effective than ACTH for infantile spasms due to cerebral malformations or tuberous sclerosis, whereas ACTH proved more effective in perinatal hypoxic–ischaemic injury patients. The efficacy of the two drugs was similar in cases of unknown cause. Disappearance of interictal EEG abnormalities occurred sooner in patients randomised to ACTH than in those who received vigabatrin as initial therapy.

In the multicentre randomised controlled UKISS trial (O’Callaghan et al. 2004; Lux et al. 2005; Riikonen 2005), proportions with no spasms on days 13 and 14 were: 40 (73%) of 55 infants assigned hormonal treatments (prednisolone 21/30, tetracosactide 19/25) and 28 (54%) of 52 infants assigned vigabatrin (difference 19%, 95% confidence intervals 1–36%, P=0.043). Two infants allocated to tetracosactide and one allocated to vigabatrin received prednisolone. Adverse events were reported in 30 (55%) of 55 infants on hormonal treatments and 28 (54%) of 52 infants on vigabatrin. When the same groups of patients were assessed at 12–14 months of age (Lux et al. 2005), the absence of spasms at final clinical assessment was similar in each treatment group (hormone 41/55 [75%] versus vigabatrin 39/51 [76%]).

Neurodevelopment was also evaluated in this follow-up study, using the Vineland Adaptive Behaviour Scales (VABS). Mean scores did not differ significantly [hormone 78.6 (standard deviation 16.8) versus vigabatrin 77.5 (standard deviation 12.7)]; except for infants with no identified underlying aetiology, in whom the mean VABS score was higher in those allocated to hormone treatment than in those allocated to vigabatrin.

Vigabatrin seems highly effective in epileptic spasms due to tuberous sclerosis (Chiron et al. 1990, 1997) and is currently the drug of choice in such cases, whereas hormonal treatment is still advised by some (Riikonen 2005) in cryptogenic cases. Interpretation of differences is challenging, and the initial use of vigabatrin is still preferred by the present authors because of its rapid action (efficacy on seizures can be evaluated in less than a week in many cases) and the high tolerance. Suggested dose is 100–150mg/kg/day. In cases where vigabatrin remains without effect after a few days, trial steroid treatment is the next choice (Arzimanoglou et al. 2004).

The most worrying side effect of vigabatrin is constriction of the visual field, which occurs in up to 30–50% of adult patients and may not regress. Its frequency has varied considerably among series. Vanhatalo et al. (2002) found that 17 (18.5%) of 91 children exposed to the agent had restriction of the temporal field. There was a positive correlation between field loss and both duration and dose of treatment. The shortest duration of vigabatrin treatment associated with visual field constriction was 15 months, and the lowest total dose 914g. Hammoudi et al. (2005) found that contrast sensitivity and visual acuity were reduced in a series of 28 children.

A Finnish study reported visual field defects in a cohort of 35 school-age children who had never received the drug in infancy and were treated for infantile spasms (Riikonen et al. 2015). Typical vigabatrin-attributed visual field defects (VFDs) were found in 11 of 32 (34%) children: in one of 11 children (9%) who received vigabatrin for less than 1 year, in three of 10 children (30%) who received vigabatrin for 12–24 months, and in seven of 11 children (63%) who received vigabatrin treatment for longer than 2 years (group 3). VFDs were mild in five and severe in six children. Patients with tuberous sclerosis were at higher risk of VFDs (six out of ten children).

The severity of the defect is usually mild, and it seems unlikely that short-term treatment (less than 6 months) will produce a severe defect, so we believe the balance of risks in a severe condition like infantile spasms still favours the use of the drug as a first choice treatment.

Other antiepileptic agents
Recurrents of epileptic spasms are not rare with either hormonal or vigabatrin therapy, and the optimal duration
of treatment remains undefined. Other forms of treatment include the benzodiazepines, especially nitrazepam. These are sometimes effective against clinical spasms (Chamberlain 1996) but their effect on the EEG abnormalities is limited. One comparative study found no difference between nitrazepam and hormonal treatment (Dreifuss et al. 1986) but most authors regard this treatment as less effective.

Sodium valproate in high doses (100–200mg/kg/day) has produced good results according to some investigators (Siemes et al. 1988; Prats et al. 1991; Ohtsuka et al. 1994), with control of the spasms in 40–65% of cases. Zonisamide may also prove to be an interesting choice, according to a rather large experience of Japanese colleagues (Tsuji et al. 2007).

In 2015, the ILAE published the results of an international survey on global treatment practices to control infantile seizures (Wilmshurst et al. 2015a). Epileptic spasms are managed with ACTH at most centres (42%) versus vigabatrin (22%), or prednisone (14%). In contrast, 88% of respondents from Oceania use oral prednisone (odds ratio 28.362, confidence interval 8.466–95.010; P<0.001). Respondents noted that their management was aetiology driven; for example, there is evidence to support the first-line use of vigabatrin for patients with tuberous sclerosis complex who develop epileptic spasms. Others noted a role for the ketogenic diet and sulthiame. Duration of treatment practices varied from 3 months to 2 years, but these conflicting responses are likely to be related to confusion over the need to respond to the seizure type management itself (the epileptic spasms) versus an underlying disease process are likely to evolve further, especially to Lennox–Gastaut syndrome.

The prognosis of infantile spasms with ACTH/steroids or vigabatrin treatment depends on aetiology, with better results in cryptogenic (or idiopathic) cases with a normal development before spasm onset. The occurrence of prior seizures, neurological signs and major MRI abnormalities predicted a poor outcome. The eventual effect of treatment choices on global developmental outcome has not been properly assessed due to the heterogeneous basis of West syndrome.

**Surgical Resection**

Surgical resection of localised brain areas of cortical dysplasia responsible for the spasms has been performed (Chugani et al. 1990; Shields et al. 1992; Chugani and Pinard 1994; Jonas et al. 2005; Kang et al. 2006) and may be indicated as early treatment in selected cases, particularly when a clearly identifiable dysplastic lesion is detectable by MRI or with hemimegalencephaly. Clinicians should be particularly attentive for asymmetrical spasms, focal neurological signs or lateralised EEG abnormalities (which might require expertise given the chaotic EEG presentation early in the course of the disorder).

Defining abnormal cortex is often possible by MRI but positron emission tomography (PET; Chugani et al. 1996), or single photon emission computed tomography (SPECT; Miyazaki et al. 1994) are often complementary. However, transient PET abnormalities, especially during the period of active hypsarrhythmia may occur (Watanabe et al. 1994), and when functional imaging abnormalities are found, repetition of the MRI and careful re-analyses of video-EEG findings should be performed looking for convergent features. Identification of, and possible preventive treatment for infants with neonatal difficulties at risk of developing infantile spasms have been attempted (Okumura and Watanabe 2001).

Multistage surgery may also need to be considered as the full anatomical extent of the underlying lesion may not be appreciated in the first 2 years of life. This is especially true for cortical malformations which may not be imaged fully on MRI due to immature myelination. However, the greater potential for neural reorganisation after surgical lesioning in early life argues more strongly for earlier and more complete one-stage ablation, especially if the seizure-onset zone is documented to involve eloquent cortical regions.

**Syndromes Closely Related to Infantile Spasms**

**Early myoclonic encephalopathy (EME) and Ohtahara syndrome or early infantile epileptic encephalopathy**

Syndromes closely related to infantile spasms include neonatal myoclonic encephalopathy, first described by Aicardi and Goutières (1978) as early myoclonic encephalopathy (EME) and Ohtahara syndrome or early infantile epileptic encephalopathy (EIEE), originally described by Ohtahara et al. (1976) (Table 16.12). In the 2005 edition of Epileptic Syndromes in Infancy, Childhood and Adolescence (John Libbey Eurotext editions), the two authors together discussed the common and specific features of the two entities, also discussing the possibility that they belong to a spectrum of disorders (Aicardi and Ohtahara 2005). Another entity, described by Gobbi and colleagues, is the syndrome of periodic spasms (Gobbi et al. 1987) is clinically characterised by repetitive lateralised spasms often following a focal seizure, can be observed at any age and is almost always due to brain malformations or extensive brain damage.

**Neonatal (or early) myoclonic encephalopathy (EME)** (EIEE) is an extremely severe condition of very early onset, characterised by partial or fragmentary erratic myoclonus from birth, marked hypotonia, and often the late occurrence of repetitive tonic spasms. The EEG consistently shows a suppression-burst pattern, characterised by a succession of bursts of paroxysmal activity interspersed with episodes of flat or low-amplitude tracing. The course is severe, neurological development remains absent or rudimentary, and death supervenes in about half the cases, most often in the first year of life (Aicardi and Ohtahara 2005). Non-ketotic hyperglycinemia is a major cause.

**Early infantile epileptic encephalopathy (EIEE)**, also known as Ohtahara syndrome (Aicardi and Ohtahara 2005), is characterised by a very early onset, frequent tonic spasms, and a suppression-burst EEG pattern. It is closely related to infantile spasms, of which it may be regarded as a neonatal form. It usually does not include myoclonus and is compatible with survival with neurological and cognitive sequelae.
All three syndromes are of lesional or metabolic origin and share a poor prognosis. Although EIEE is thought to be mostly due to brain malformations and EME to metabolic disorders, there are many exceptions and migration disorders have been shown to cause myoclonic encephalopathy (Du Plessis et al. 1993). Moreover, cases of glycine encephalopathy may present with severe neonatal encephalopathy but without myoclonic phenomena, suggesting that there is no strict relationship between aetiology and clinical features (Aicardi and Ohtahara 2005). Thus, the separation between EIEE and neonatal myoclonic encephalopathy may be artificial (Lombroso 1990), and EIEE may be an early form of infantile spasms. As underscored in a recently published comparative table and comment (Mizrahi and Milh 2012), whether the two entities represent two aspects of a continuum of one disorder remains an open question, awaiting prospective study from an electroclinical perspective with well-studied pathology and genetic screening.

Known genetic causes of early-onset epileptic encephalopathies with burst suppression include brain malformations (e.g. polymicrogyria and lissencephaly), inborn errors of metabolism (e.g. pyridoxine- and other vitamin-dependent epilepsies, mitochondrial disorders, and amino acidopathies), and other genetic aetiologies (e.g. pathogenic variants in ARX, KCNQ2, SCN2A, SIK1, SLC25A22, STXBPI). Genotype–phenotype correlations in 33 patients with a referral diagnosis of Ohtahara syndrome or early myoclonic encephalopathy without malformations of cortical development were investigated by exome sequencing (Olson et al. 2017). In 17 of 28 (61%) patients with confirmed early burst suppression, the authors identified variants predicted to be pathogenic including KCNQ2 (n=10), STXBPI (n=2), SCN2A (n=2), PNPO (n=1), PIGA (n=1) and SEPSECS (n=1). In three of five (60%) patients without confirmed early burst suppression, they identified variants predicted to be pathogenic in STXBPI (n=2) and SCN2A (n=1). The patient with the homozygous PNPO variant had a low cerebrospinal fluid pyridoxal-5-phosphate level. Otherwise, no early laboratory or clinical features distinguished the cases associated with pathogenic variants in specific genes from each other or from those with no prior genetic cause identified.

Dentato-olivary dysplasia (Harding and Boyd 1991) is a rare cause of neonatal tonic seizures and possibly infantile spasms. The prognosis is very poor and the diagnosis is possible only at autopsy. One familial case is known (Harding and Copp 1997).

### Lennox–Gastaut and Related Syndromes

The Lennox–Gastaut syndrome (LGS) includes patients with epilepsy starting mainly between ages 1 and 7 years who present with tonic, atonic and myoclonic seizures resulting in multiple falls and atypical absences, and whose interictal EEGs contain bilateral, though not necessarily symmetrical, slow (≤2.5Hz) spike–wave activity. The limits of LGS are variably understood by different investigators who use diverse criteria for its definition and for its separation from related syndromes such as the myoclonic epilepsies (for a discussion on the nosology of the syndrome, see Aicardi and Levy Gomes 1988, 1989; Arzimanoglou et al. 2004, 2009).

Most investigators now accept the definition proposed by Beaumanoir and colleagues (Beaumanoir and Dravet 1992; Beaumanoir and Blume 2005), that is, of a syndrome of multiple seizure types with interictal slow spike–waves, spikes and bursts of 10–20Hz spikes during sleep, most often associated with intellectual disability.

The seizures of LGS include ‘core’ seizures (myoatonic and tonic, atypical absences and episodes of nonconvulsive status epilepticus) that are variably associated with less characteristic seizures such as tonic, clonic, focal or unilateral seizures.

**Tonic seizures**, considered by most authors as a marker of the syndrome, are encountered in 55–92% of cases. Clinically, they are marked by body stiffening involving axial and proximal limb muscles, with extension more commonly than flexion of the trunk, lower limbs and arms. They may be limited to the trunk and neck, with opening of the eyes and, frequently,
apnoea. They sometimes consist only of eye opening with mild ‘stretching’ movements. Their duration does not exceed 30 seconds and is often no more than 10 seconds. Even in such cases, the contraction is clearly tonic, resulting in sustained clinical and electromyographic muscle activity (Aicardi and Levy Gomes 1988; Arzimanoglou et al. 2009). The ictal EEG shows generalised fast frequencies (≥10Hz) of increasing or high amplitude (Beaumanoir and Dravet 1992; Arzimanoglou et al. 2004; Beaumanoir and Blume 2005), sometimes followed by a few spike–wave complexes. Similar brief duration discharges without clinical manifestations are recorded during slow sleep. Tonic seizures are often nocturnal but their manifestations in sleep may be so mild that they are unnoticed (Beaumanoir and Blume 2005; Arzimanoglou et al. 2009).

Atonic seizures occur in 26–56% of LGS patients. They consist of abrupt muscle relaxation and are a common cause of falls in such children, although tonic and myoclonic seizures also produce falls. Atonic seizures represent a major practical problem as they often cause injuries and are not easily prevented by wearing a helmet. The mechanisms of falls are often unclear when no polygraphic recording is available, making the noncommittal term of atonic seizure preferred. Most atonic seizures are associated with loss of consciousness, and it is not clear whether they are purely atonic or are associated with tonic phenomena. Most have the same EEG concomitants as tonic seizures. Thus, they seem to differ from pure atonic seizures associated with bursts of spike–wave activity as observed in the myoclonic–astatic epilepsies (Oguni et al. 1993, 1996, 2001a).

True myoclonic seizures occur in up to 28% of cases and are also associated with falls. The type of seizure observed depends on the age at onset of LGS. In cases of early onset, tonic seizures predominate, whereas myoclonic jerks and absences are more frequent in late-onset cases (Chevrie and Aicardi 1972, 1996). Atypical absences are present in 17–60% of patients. Although their onset and termination may be more progressive than in typical absences (see below), they are marked by the same interruption of awareness and responsiveness with only mild motor components (stiffness, hypotonia, simple automatisms) and their recognition depends on the clinical context and the EEG concomitants. These are sometimes ictal slow spike–waves that are difficult to distinguish from interictal spike–waves, but more often consist of fast discharges similar to those associated with tonic seizures.

Episodes of nonconvulsive status epilepticus are frequent (Dravet et al. 1986; Beaumanoir et al. 1988) and may last several days or even weeks. They may be responsible for alternating good and bad periods with considerable changes in reaction time and cognitive activity. The most common type is characterised by the alternation of tonic seizures with episodes of confused behaviour, often with erratic myoclonic activity of the face and upper limbs that last from hours to weeks (Arzimanoglou et al. 2009).

The interictal EEG in LGS reveals a diffuse slow spike–wave pattern with slow blunted spikes followed by irregular 1–2Hz slow waves of variable amplitude, usually on a slow, irregular background. The discharges may be asymmetrical and are often subclinical. They show little or no response to hyperventilation or photic stimulation but activate during drowsiness and sleep (Aicardi and Levy Gomes 1988). Runs of 10–20Hz rhythms lasting several seconds occur during non-rapid eye movement (REM) sleep that are likely to represent subclinical or minimal tonic seizures (Fig. 16.7a, b). At the same stage, slow spike–wave complexes are frequently replaced by polyspike–wave complexes. Multifocal discharges may also occur.

Intellectual disability is present before onset of seizures in 20–60% of cases (Arzimanoglou et al. 2006, 2009), as aetiology plays a major role. The proportion of patients with intellectual impairment increases with the passing of time, rising to 90% 5 years after onset (Chevrie and Aicardi 1972). Children having experienced infantile spasms at onset who later develop LGS syndrome also have intellectual disability. Clear loss of skills is observed in some patients. Psychotic symptoms are often present.

The aetiology of LGS is heterogeneous. Brain lesions play an important role, whereas genetic factors are regarded as less important. Up to two-thirds of cases may result from a demonstrable brain abnormality or occur in patients with previous developmental delay, and these are termed symptomatic. A significant proportion of LGS cases follow infantile epileptic spasms, with a gradual transition, and are due to the same brain insults that produced the spasms. Brain malformations, however, are less common in LGS, and LGS has been only exceptionally recorded in the course of Aicardi syndrome and of lissencephaly. Focal or multifocal abnormalities of cortical development are frequent, and cases of band heterotopia and of bilateral perisylvian syndromes are on record (see Chapters 1 and 3). Tuberous sclerosis and less common neurocutaneous disorders, such as linear nevus sebaceous syndrome and hypomelanosis of Ito (personal cases), may also be responsible (see Chapter 4). Acquired destructive lesions are less common. Metabolic diseases are exceptional, although LGS due to Leigh encephalomyelopathy has been recorded (Matsuishi et al. 1985). Rare cases of LGS secondary to brain tumours are reported (Honda et al. 1985).

A proportion of cases have no obvious recognised cause and are considered cryptogenic. The occurrence of LGS in patients with unilateral lesions has led to attempts at distinguishing true LGS from bilateral secondary synchrony (Gastaut and Zifkin 1988). In fact, cases of secondary bilateral synchrony fulfil criteria for diagnosing LGS, and their recognition raises the possibility of surgery. PET studies reveal several metabolic patterns (focal, multifocal or diffuse) that correspond to different mechanisms (Chugani et al. 1987; Linuma et al. 1987; Theodore et al. 1987). Their practical significance is still unclear as the criteria for the diagnosis of LGS was variable within this series.

The diagnosis of LGS is not difficult if strict criteria are applied and the progressive course of the disorder, at least in its initial phases, is considered. Differentiating LGS from other syndromes associated with falls may be challenging, particularly in the early stages or if tonic seizures have not occurred (Arzimanoglou et al. 2009). Rare cases of atypical benign
epilepsy of children, also called Aicardi-Chevrie syndrome (Aicardi and Levy Gomes 1992) or pseudo-Lennox syndrome (Hahn 2000), in which repeated falls and diffuse paroxysmal EEG activity during sleep may mimic LGS and are a source of clinical confusion. Such cases may run a relatively benign course and should be differentiated.

The prognosis of LGS is poor (Arzimanoglou 2003, 2009). Approximately 80% of patients continue to have seizures and, due to seizures or cognitive deterioration, very few patients live independent lives. Outcome is especially poor for patients with brain damage, early seizure onset or antecedents including infantile spasms, or the presence of intellectual disability.
before the seizure onset. Less than 10% of patients have a normal intellectual level. It is difficult to distinguish these cases from those with less favourable outcome, although a later age at onset, a positive response to hyperventilation and a higher incidence of 3Hz spike-wave complexes carry more positive prognostic value. Cases with these features have been termed ‘intermediate petit mal’ but the separation of this subgroup is debatable as the diagnostic criteria are similar to LGS. In typical cases the clinical pattern changes with age and overall seizure frequency usually diminishes between ages 15 and 20 years. Atypical absences and drop attacks may become rare but other seizure types, including tonic seizures in sleep, often persist. Tonic seizures during sleep are probably underreported for older patients by their parents (Beaumanoir and Blume 2005; Arzimanoglou et al. 2009).

The treatment of LGS is often unsatisfactory, even in experienced hands. This is directly related to the various aetiologies underlying the syndrome and the presence of multiple types of seizures that respond differently to the AEDs prescribed. The most recent Cochrane review (Hancock and Cross 2013) listed only nine randomised controlled trials and concluded that it was not possible to proceed to meta-analysis as the trials studied different populations, utilised different therapies and measured different outcomes. From our point of view another criticism is that patients are enrolled in the studies too late in the course of the disorder, when intellectual disability and multiple seizure types are already established. The lack of biomarkers is an important reason that a confident diagnosis cannot be established early in the course of the disorder. Thus, the trials only provide selective information on the control of a given seizure type, without addressing the overall evolution of the syndrome.

As a result, treatment is based on clinical experience or uncontrolled studies. Among conventional AEDs, combinations of sodium valproate and a benzodiazepine are most beneficial, but all medications may be worth trying in individual patients. Lamotrigine is reported to be efficacious (Motte et al. 1997) especially against atonic seizures. In our experience, an association of lamotrigine and sodium valproate is probably the best treatment combination currently available and should be tried early. Titrination of lamotrigine should be done slowly to diminish the risk of an allergic reaction. Topiramate (Sachdeo et al. 1999) and rufinamide (Glauser et al. 2008; Otsuka et al. 2014; Arzimanoglou 2016) were also shown to be effective in randomised controlled or open trials.

Carbamazepine is deemed satisfactory by some clinicians for focal and tonic seizures but may have no effect or even aggravate other seizure types, such as myoclonic seizures or atypical absences. Because of its lack of interactions with other AEDs, vigabatrin has been used with some measure of success, particularly in LGS patients combining focal seizures with the core seizures of the syndrome. Felbamate, particularly when used in accordance with existing recommendations and close monitoring, should also be considered despite possible toxicity (Pellock et al. 2006; Heyman et al. 2014; Shi et al. 2014).

Interestingly, combinations of drugs are often required as individual drugs may have a specific activity against only certain types of seizures. A working knowledge of AED interactions (see Zaccara and Perucca 2015) is required, and children should be treated by child neurologists who specialise in epilepsy.

Surgery is an option, particularly in lesional cases such as cortical dysplasias, following the usual presurgical evaluation processes to be performed within comprehensive epilepsy programmes. Callosotomy is often effective for seizures associated with falls that cause craniofacial trauma (Jackson et al. 2015).

Because of the high rate of drug failure, other treatments may be worth trying even late in the course of the disorder. The ketogenic diet has favourable short-term effects despite unpalatability and side effects (Kossoff and Shields 2014). Vagus nerve stimulation may also be an alternative (Orosz et al. 2014; Kossoff and Shields 2014). Corticosteroids are used to stabilise very active epilepsy or status epilepticus. Intravenous immunoglobulins have been advocated but have not been properly tested. Thyrotropin-releasing hormone (Matsumoto et al. 1987) has been used, mainly in Japan.

A consensus approach reviewed issues associated with the diagnosis and treatment of LGS (Arzimanoglou et al. 2009). The limitations and difficulties of clinical trials were emphasised and a comprehensive approach for the treatment of this syndrome was proposed. Irrational polytherapy, combining three to four and sometimes more AEDs should be avoided.

Dravet Syndrome

The syndrome was initially described by Dr Charlotte Dravet as severe myoclonic epilepsy of infants (Dravet 1978, 1982). Although it does often feature myoclonic phenomena, only uncommonly are these the first manifestation of the syndrome. As suggested by clinical observations (Veggiotti et al. 2001), progress in molecular genetics has confirmed that Dravet syndrome is part of a continuum of severe epilepsies of infancy that may or may not feature additional generalised tonic-clonic seizures, focal seizures, atypical absences and myoclonias (Arzimanoglou 2009). Dravet syndrome can be considered as the most severe end of the spectrum of epilepsy syndromes classified as ‘generalised epilepsy with febrile seizures (GEFS+)’ (see below). Although the recognition of Dravet syndrome has increased in the last decade, it remains a rare disorder (incidence estimated less than one per 20,000 to 40,000; prevalence in the United States lower than 10,000 cases). It is classified as ORPHA 33069 (Orphanet classification).

Dravet syndrome is caused by new mutations in the sodium channel gene SCN1A in over 70–80% of cases (Claes et al. 2001). No mutations of the SCN1A gene are present in the remaining 20%. Two familial cases of GABRG2 mutations have been reported.

Symptom onset usually occurs between ages 4 and 10 months and is characterised by clonic seizures, that are often unilateral and prolonged and precipitated by fever in 75% of cases. Seizures recur several times, at short intervals (usually less than 2 months). Initial development is normal but other seizure types appear during the second or third year including
focal seizures, atypical absences, myoclonic jerks and noncon- 
volusive status. At the same time, cognitive slowing becomes 
evident and pyramidal tract signs and ataxia often supervene.

Intercital EEG recordings are generally normal during 
the first months of the disorder despite frequent seizures. 
After the second year of life, the EEG does not show slow 
spike–wave complexes but rather bursts of fast spike–wave 
complexes, often associated with multifocal spikes. Photo- 
sensitivity occurs in 25% of patients, and self-precipitation of 
seizures is common. The long-term outcome is poor. Seizures 
persist mainly as tonic–clonic and myoclonic seizures tend to 
disappear. Intellectual disability of variable degree is constant 
(Ogino et al. 1989; Watanabe et al. 1989), epilepsy with hemi-grand mal and high-amplitude EEG slow 
waves (Doose 1992) or idiopathic epilepsy of infancy (Ebach 
et al. 2005). Such forms have been grouped (Ogini et al. 
2001a; Fukuma et al. 2004) as ‘‘borderline cases’’ of severe 
myoclonic epilepsy. The course of such cases appears similar 
to the typical form, although less severe.

The identification of mutations in other genes in the 
remaining 20–30% of SCN1A-negative Dravet syndrome 
patients has failed to locate other genes except for a GABRG2 
gene mutation and a SCN1B mutation found in single 
patients. The recent identification of protocadherin 19 
(PCDH19) mutations in SCN1A-negative Dravet syndrome 
patients could account for 5% of all Dravet syndrome patients, 
because their clinical pictures shared with those of the Dravet 
borderline phenotype (Depienne et al. 2010). In another 
study, seven (37%) of 19 patients with SCN1A-negative 
Dravet syndrome were found to have PCDH19 mutations 
(Marini et al. 2010). Further studies to investigate the molec- 
ular and cellular basis of epileptogenesis in Dravet syndrome 
have been performed in animal models of severe myoclonic 
epilepsy of infancy, and SCN1A knock-out and knock-in 
mouse models were developed.

The identification of genes associated with Dravet 
syndrome and related syndromes hints at their com- 
plexity. Early identification of SCN1A mutations is useful to 
support an early diagnosis of Dravet syndrome, facilitate 
counselling, and avoid AEDs with adverse effects. However, 
the defining characteristics of seizure type and EEG patterns 
initially identified by Dravet remain fundamental to diagnosis 
(Arzimanoglou 2009). Therapies for Dravet syndrome is disappointing, although 
occasional cases with a satisfactory outcome with high-dose 
sodium valproate are reported. Our practice is to initiate 
treatment with sodium valproate rapidly in association with a 
benzodiazepine, with a preference for clobazam. If seizures 
persist we strongly recommend the introduction of stiripentol in 
countries where it is available. Stiripentol (Chiron 2007) 
was granted orphan drug status in the European Union for the 
treatment of Dravet syndrome, following a study where it 
was used in combination with sodium valproate and cloba- 
zam (Chiron et al. 2000). The interactions of stiripentol with 
many other drugs need to be carefully considered. Although 
complete control is rarely reached, this association reduces 
both the frequency and the duration of convulsive episodes in 
most of the cases.

Among the most recent AEDs, several open-label studies 
showed that topiramate may lead to relatively good control of 
convulsive and focal seizures. Levetiracetam and zonis- 
amide are alternative options. Ethosuximide can prove useful 
when myoclonic seizures are very frequent. Bromides are also 
employed, particularly in Germany and Japan. Vigabatrin is 
efficacious in patients with attenuated myoclonic compo-

iments. Lamotrigine reportedly aggravated seizures in young 
children (Guerrini et al. 1998b) but can be administered safely
with acceptable results in older patients, often in combination with sodium valproate. The respective place of ketogenic diet and vagus nerve stimulation (VNS) are unknown, but are alternative options. Trials with cannabidiol or fenfluramine are ongoing. Similar to LGS drug choices should be made by experienced paediatric epileptologists.

**Malignant Migrating Partial Seizures in Infancy**

Malignant migrating partial seizures in infancy (MMPSI) is a rare and easily overlooked disorder (Coppola et al. 1995; Coppola 2013). Early diagnosis is based on seizure onset in the first 6 months of life, multiple types of seizures occurring independently and even simultaneously migrating between cortical areas in one or both hemispheres. Clinical diagnosis also depends on the functional features of the involved cortex, absence of a significant family history, and lack of an established aetiology.

At onset, the paroxysmal events may be misinterpreted as nonepileptic phenomena because of the combination of autonomic manifestations (apnoea, flushing) and focal motor events. Rapidly (from 3 weeks to 10 months of age) a ‘stormy phase’ is observed, as seizures become very frequent and polymorphous, occurring in clusters of 5–30 several times a day or near-continuous for days or weeks. Seizure semiology mostly includes lateral head and eye deviation, eyelid twitches, unilateral or bilateral clonic or tonic limb movement, apnoea, facial flushing, chewing movements, mastication, and secondary tonic–clonic generalisation (Coppola et al. 1995).

Focal ictal EEG discharges typically migrate, beginning in one cortical area and either remaining localised or expanding to contiguous regions; other seizures develop independently in different areas of the same or opposite cerebral hemisphere (Caraballo et al. 2008; Coppola 2013).

Seizures in MMPSI are highly drug resistant. In his last review, Coppola discussed the use of bromides (60–80mg/kg/day) and stiripentol, clobazam and levetiracetam (Coppola 2013). The ketogenic diet and VNS therapy yielded poor results.

The long-term outcome of psychomotor development and cognitive function in MMPSI remains poor. Between clusters of seizures, patients remain floppy, drooling, drowsy, and unable to drink or swallow. Limited recovery is observed after clusters, usually consisting of visual tracking without reaching for objects. Major axial hypotonia, pyramidal and extrapyramidal signs with athetotic movements develop progressively.

The potential role of a gene mutation coding for some ion channels is gaining clinical acceptance. The initial mutational scanning of \( KCNQ2, KCNQ3, SCN1A, SCN2A, CLCN2 \) and \( MECP2 \) genes did not disclose any mutations. However, almost half of sporadic MMPSI cases show mutations in \( KCNT1 \), resulting in a gain-of-function of this non-conducting potassium channel that is involved in developmental signalling pathways (Barcia et al. 2012). A small number of other children have mutations in the \( SCN1A \) gene; one patient presented with an inherited homozygous deletion disrupting the \( PLCB1 \) gene (for reviews see Coppola 2013; Striano et al. 2013). A mutation in the \( TBC1D24 \) gene, an ARF6-interacting protein, was identified in two affected siblings but was not confirmed in others. Similar discordances are observed in reports discussing the role of a novel homozygous mutation in the \( SLC25A2 \) gene (Poduri et al. 2013; Striano et al. 2013).

**Epilepsies and Syndromes of Infancy and Early Childhood with Predominantly Myoclonic Seizures**

Epilepsies that consist mainly of true myoclonic seizures—that is, seizures marked clinically by very brief shock-like muscle contractions and, electrically, by fast spike–wave or polyspike–wave complexes—occur mostly in infancy and early childhood (Aicardi 1996; Guerrini and Aicardi 2003; Arzimanoglu et al. 2004). These epilepsies may sometimes be confused with the LGS because of the frequent repetition of brief episodes associated with multiple falls, the presence of spike–wave discharges in both groups, and the frequent association of intellectual disability or regression associated with the seizures. However, the clinical and EEG manifestations of the myoclonic epilepsies clearly differ from those of LGS, and the outlook for control of seizures and cognitive development may not be the same.

Myoclonic seizures consist of sudden, lightning-like muscle contractions that may involve the whole body (massive myoclonic seizures) or be limited to the upper limbs, face or eyelids. The jerks are usually symmetrical but may be unilateral or localised to small muscle groups. The ictal EEG shows polyspike–wave paroxysms. Ictal electromyography demonstrates an extremely brief muscle contraction followed by a period of inactivity lasting 100–350ms. When this period is relatively long, muscle resolution may become clinically evident, resulting in a myatonic seizure (Oguni et al. 1994, 1997). Occasionally, only the atonic phase is detectable, the so-called negative myoclonus (Guerrini and Aicardi 2003). Clinically, atonia of variable intensity and duration often follows the myoclonic jerk. When generalised and long enough, it results in falls (drop attacks), and the differentiation of atonic from myoclonic seizures may therefore be clinically impossible. Myoclonic–astatic epilepsy should therefore be considered as a variant of myoclonic epilepsy in which the atonic component is particularly obvious.

The nosology of the myoclonic epilepsies remains unclear. The ILAE International Classification identifies three major groups within this age group: severe myoclonic epilepsy or Dravet syndrome of earlier onset, myoclonic epilepsy of infancy, and epilepsy with myoclonic–astatic seizures (first described by Doose 1992). A number of cases of myoclonic epilepsies in infancy and early childhood remain unclassified,
and intermediate forms between the different syndromes exist (Arzimanoglou et al. 2004). They must be distinguished from other syndromes with frequent brief episodes and repeated falls. Particularly in very young infants, when the electro-clinical presentation does not fully correspond to the classic descriptions discussed below, aetiological screening (including metabolic disorders) is indicated. Myoclonic seizures are also a prominent feature of some of the neuronal ceroid-lipofuscinoses (see Chapter 10). The associated symptoms usually alert the treating physicians.

Myoclonic (Benign) Epilepsy of Infancy

Myoclonic epilepsy of infancy (MEI) was first described by Dravet and Bureau in 1981. The syndrome is characterised by brief myoclonic seizures, spontaneous or provoked by noise or contact, starting between the ages of 4 months and 3 years in otherwise neurodevelopmentally typical children, predominantly in boys (Dravet et al. 1992, 2005). Myoclonic seizures are the single presenting seizure type, with the exception of rare simple febrile convulsions. The interictal EEG, including sleep organisation, is normal, and spontaneous spike–wave discharges are rare. Myoclonias are associated with EEG discharges, in the form of fast generalised spike–wave or polyspike–waves greater than 3Hz and of similar duration as the myoclonias. The course of the epilepsy is benign with a good response to monotherapy with sodium valproate and, when indicated, the association of ethosuximide or a benzodiazepine. Levetiracetam is another possible first option. The active phase of the syndrome is limited to a few months, but in the absence of evidence-based guidelines expert clinicians continue AED treatment for 2–3 years. Global cognitive outcome is less favourable than initially believed (Guerrini et al. 2012; de Bellescize et al. 2015) as mild learning or behavioural difficulties and neurodevelopmental delay may occur.

It is still not clear whether the term ‘benign myoclonic epilepsy’ should be limited to cases exclusively with myoclonic seizures. Aicardi and Levy Gomes (1989) reported 19 young children, mainly boys with a high frequency of familial antecedents of seizures and infrequent tonic–clonic seizures and/or brief absences in addition to frequent myoclonic jerks and a relatively favourable outcome. Such cases suggest the existence of a spectrum of nonlesional, probably genetically determined, myoclonic epilepsies. In some infants, seizures are precipitated by sudden exteroceptive or proprioceptive stimuli. This ‘touch’ or reflex myoclonic epilepsy (Ricci et al. 1995) has an excellent prognosis and treatment may be avoided. Cases like MEI may also occur in older children, and the syndrome is likely to be an early expression of an idiopathic generalised epilepsy, the infantile equivalent of juvenile myoclonic epilepsy.

The genetics of MEI are unknown. Cases are rare and no familial cases of MEI have been described. Arzimanoglou et al. (1996) described a family in which the proband had epilepsy with myoclonic–astatic seizures and his younger brother experienced typical MEI with excellent outcome.

Myoclonic–Astatic Epilepsy

Myoclonic–astatic epilepsy (probably more appropriately epilepsy with predominantly myoclonic–astatic or atonic seizures) is perhaps better regarded as a category of generalised nonlesional myoclonic epilepsies rather than a discrete syndrome (Guerrini and Aicardi 2003; Arzimanoglou et al. 2004; Guerrini et al. 2005). The term ‘myoclonic–astatic’ was first used by Doose et al. (1970) in a manuscript on ‘centrencephalic myoclonic–astatic petit mal’ and further developed in by Doose and Baier (1987) in a paper entitled ‘Genetic factors in epilepsies with primarily generalised minor seizures’. It was initially defined as a form of genetically determined, nonlesional generalised epilepsy, and probably included cases that are now termed severe or benign myoclonic epilepsy as well as cases fulfilling the current concept of myoclonic–astatic epilepsy (Guerrini and Aicardi 2003).

Onset is later than for Dravet syndrome, usually between 1 and 5 years of age, and it occurs more often in boys. It is characterised clinically by the predominance of purely myoclonic and/or myoatonic seizures (Fig. 16.8a, b); the seizures may result in falls or produce only a series of head drops and/or sagging at the knees when brief. Other seizure types are often associated, including generalised tonic–clonic seizures, atypical absences and episodes of nonconvulsive status epilepticus. Tonic seizures are unusual but are relatively frequent in some series (Kaminska et al. 1999; Oguni et al. 2001a). The latter authors found them to be present in up to two-thirds of their cases, a finding probably reflecting the nosological uncertainties mentioned above. Astatic seizures (drop attacks) may have different mechanisms (myoclonic, astatic or tonic) that are indistinguishable without polygraphic recording. Tonic seizures may be more frequent in children with an unfavourable outcome, but also occur in almost 30% of cases with a favourable outcome (Kaminska et al. 1999). Differentiating MAE from LGS may be difficult during the early stages of the disorder.

The EEG shows fast (≥3Hz) generalised spike–wave or poly-spike–wave discharges of short duration (usually less than 4–5 seconds). Doose emphasised the presence of bi-parietal theta rhythms.

Genetic factors play an important role and several children with MAE belong to large generalised epilepsy with febrile seizures plus (GEFS+) families with missense mutations of the SCN1A gene. AED-resistant cases should be screened for GLUT-1 deficiency (Mullen et al. 2011).

Remission within a few years with normal cognition occurs in almost 60% of cases (Oguni et al. 2001a; Guerrini et al. 2005). However, at onset, falls are often difficult to control and result in serious injury. In our experience the initial presentation is often ‘stormy’, with repeated drop attacks. However, a severe onset does not necessarily predict a poor outcome. Other patients run an unfavourable course with frequent seizures and learning difficulties (20%) or intellectual disability (20%) but outcome is unpredictable at symptom onset.
Figure 16.8  (a) Atonic seizure. EEG discharge starts with brief burst of fast rhythm, followed by a few spike–wave complexes and by slow waves. EMG trace shows disappearance of normal tonic activity during EEG discharge in posterior cervical muscles (CERVIC.R), sternomastoid (STCM.R) and deltoid (DELT.R) on right side. (Courtesy Dr J Roger, Centre Saint Paul, Marseille; reproduced from 3rd edition.) (b) Atonic seizure. Awakening EEG (150µV/cm) in a 4-year-old girl with atypical rolandic epilepsy demonstrating an atonic seizure after a polyspike. Head drop coincides with the slow wave that follows (8th second) at the moment of muscle atonia. (Courtesy Dept of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology, University Hospitals of Lyon, France.)
The effectiveness of AEDs is variable. Sodium valproate is considered a first-line agent and if needed, according to our experience, a combination of sodium valproate and lamotrigine. Ethosuximide, for myoclonic seizures and absences, or benzodiazepines, particularly clobazam, can be effective. Finally, topiramate and levetiracetam or sulthiame are important alternatives. The ketogenic diet is also an effective alternative to medication (Caraballo et al. 2006). Rufinamide and perampanel are under evaluation. Carbamazepine, vigabatrin, oxcarbazepine and gabapentin should be avoided (Arzimanoglou et al. 2004; Guerrini et al. 2005).

FOCAL EPILEPSIES OF INFANCY AND EARLY CHILDHOOD

Focal epilepsies, particularly structural, may begin at any age. Most are discussed in the Seizures and Syndromes of Late Childhood and Adolescence section.

A large proportion of seizures in the first 2 years of life cannot be categorised into a recognised epilepsy syndrome (Korff and Nordli 2006). Most are probably focal disorders although their clinical manifestations may not be localising. Their features include head and eye version or focal tonic contraction, but seizures with generalised vasomotor phenomena or diffuse tonic changes may have a focal origin, as shown on the EEG (Duchowny 1987; Rathgeb et al. 1998; Watanabe et al. 2005). Evaluation of the state of consciousness is obviously very difficult in this age range (Acharya et al. 1997). Focal seizures are often due to gross brain damage (Chevrier and Aicardi 1977, 1979; Cavazzuti et al. 1984). Duchowny (1987, 1992) reported 14 infants with complex partial seizures due to gross brain damage whose main ictal features were head version and body stiffening, very much like most cases of focal seizures of infants. Generalised seizures, which are rare in this age group, may have a better outlook in the absence of gross brain pathology (Chevrier and Aicardi 1978). The development of high-definition neuroimaging techniques has facilitated the early detection in infants of small lesions (cortical dysplasias, dysembryoplastic neuroepithelial tumours, gangliogliomas and tuberous sclerosis-related lesions) at the origin of focal seizures, which are often surgically treatable despite young age of the patients. Treatment of lesional epilepsies is discussed in a later section, as more data are available on epilepsies of late childhood and adolescence. However, it is important to underscore here that focal epilepsy in infancy may be due to identifiable small lesions, as this may influence treatment choices. Whether early surgery might modify overall cognitive outcome is currently under evaluation but as far as seizure outcome is concerned all teams with experience in epilepsy surgery favour early resection whenever feasible (Arzimanoglou et al. 2016c).

Other specific syndromes of focal seizures in infancy have been described. The rare syndrome of partial migratory seizures in infancy with malignant outcome (Coppola et al. 1995; Coppola 2013) or MMPSI was discussed in the section on Malignant Migrating Partial Seizures in Infancy (MMPSI). The syndrome is characterised by very frequent focal seizures of multiple origin and neurological deterioration leading rapidly to death. Although this syndrome has been described as a progressive condition, similar features may be obtained with fixed or progressive encephalopathies with several causes (Ishii et al. 2002).

Self-Limited (Previously Called ‘Benign’) Epilepsy Syndromes of Infancy

Recognition of benign epilepsy syndromes in infants is important, as their prognosis is much better than other types of seizures in this age range. Their frequency is not known and may be variable depending on ethnic origin.

Watanabe et al. (1987) described nine infants with complex focal seizures with a favourable course as benign complex partial epilepsy of infancy. They later described a second group of seven children who developed secondarily generalised seizures with focal onset (Watanabe 1996). More recently, Okumura et al. (2006) reviewed 33 cases and grouped them all as benign partial epilepsy in infancy. Seizures began before age 6 months in 26 cases and were infrequent (average of seven seizures). Seizures occurred in clusters and could be focal with altered consciousness, secondary generalisation or both. Seizures stopped before the age of 18 months in all cases, although a few infants experienced later febrile seizures. Seventeen infants had a family history of seizures. Several syndromes with similar characteristics are reported (see Vigevano and Bureau 2005; Chahine and Mikati 2006; de Bellescize et al. 2015).

Vigevano et al. (1992, 1994b) first described the syndrome of familial benign partial seizures of infants. This syndrome is dominantly inherited and has its onset after the neonatal period. The interictal EEG is usually normal. A few infants demonstrate small-amplitude spikes during sleep suggesting a specific syndrome (Coppola et al. 1995, 2006). Diagnosis rests on a history of similar events in relatives, consistent with an autosomal dominant transmission. In an as yet undefined proportion of cases, choreo-athetotic movements supervene in the same patients several months or years after disappearance of the convulsions (Szetowski et al. 1997; Swoboda et al. 2000) and respond well to carbamazepine.

Focal infantile convulsions are linked to several chromosomal loci including 19q and 16 but no genes are yet characterised (see Table 16.2). The subgroup of patients with movement disorder are consistently linked to centromeric chromosome 16 (Striano et al. 2006). Berkovic et al. (2004) observed an intermediate form between neonatal and infantile seizures, termed infantile–neonatal convulsions due to a mutation in the gene encoding the voltage-gated sodium channel a2 subunit (SCN2A) on chromosome 2q24 (Heron et al. 2002). Caraballo et al. (2003) studied 64 cases of infantile seizures and found no clinical differences between genetic and apparent non-genetic infantile convulsions. It is unknown
whether the clinically similar benign syndromes of infantile seizures belong to the same or different entities.

Benign seizures are also recognised in Asian patients and recently in European infants in association with benign diarrhoal disease (Lee et al. 1993; Komori et al. 1995; Imai et al. 1999).

A syndrome of benign infantile focal epilepsy with midline spike and waves during sleep was first described by Bureau and Maton (1998). Seizures occurred in wakefulness or sleep, with onset characterised by a combination of staring, psychomotor arrest, arm stiffening and loss of consciousness; cyanosis, particularly of the face, was a constant feature in all affected patients. Seizure duration ranged from 1 to 5 minutes. The waking EEG consistently showed no abnormalities, but diphasic spikes of low or medium voltage followed by a bell-shaped slow wave of higher voltage were recorded in sleep. Morphologically, these transients are readily discernible from physiological sleep vertex spikes. Seizures usually cease before age 4 years and treatment is rarely necessary (Capovilla et al. 2006).

**FEBRILE CONVULSIONS**

Febrile convulsions are epileptic seizures precipitated by fever that are not due to an intracranial infection or other definable CNS cause and are not preceded by afebrile seizures. Febrile convulsions are the single most common problem in paediatric neurology, with a total incidence of 2–5% in children under age 5 years in Western countries and up to 8% in Japan. Excellent reviews of the topic are available (Nelson and Ellenberg 1981; Wallace 1988; Baram and Shinnar 2002).

**AETIOLOGY OF FEBRILE CONVULSIONS**

Genetic factors are important in the causation of febrile convulsions, and there is a high incidence of a family history of febrile convulsions varying between 17% and 31% in first-degree relatives. Most studies suggest a polygenic mode of transmission (Rich et al. 1987). An autosomal dominant pattern, however, may be at play in probands with three or more episodes and in some families with multiple affected members and a tendency to long-lasting seizures (see also discussion below on GEFS+).

The genes responsible for febrile convulsions are probably distinct from those causing afebrile seizures (see Table 16.2). Only a small proportion of children with febrile convulsions have a first-degree relative with epilepsy (Berg et al. 1992). Febrile seizures may precede some forms of epilepsy such as childhood absence epilepsy, Rolandic epilepsy and LGS but the frequency of such an occurrence is poorly known (Arzimanoglou and Dravet 2006).

Rarely, early-onset febrile seizures are associated with de novo PRRT2 mutations which encode the proline-rich transmembrane protein 2 gene. Febrile seizure episodes are best characterised as benign familial infantile epilepsy (BFIE) with febrile seizure onset typically beginning at about 6 months of age. As the seizures in BFIE may consist of simple febrile episodes (Schieffer et al. 2012) they are often difficult to distinguish from febrile seizures due to other aetiologies.

The fever associated with febrile seizures is usually high (>38.5°C) and has the same causes as other fevers in this age group, including immunisations (Millichap and Millichap 2006). One exception may be exanthema subitum, which is associated with a higher incidence of seizures, varying between 8% and 13% (Asano et al. 1994). Gastroenteritis, on the other hand, is a relatively rare cause for the degree of temperature (Berg et al. 1995). Seizures usually occur early in the course of a fever and are actually the first symptom in 25–42% of cases. An earlier onset is noted in girls (Wallace 1988).

Prenatal and perinatal factors do not play an important role in causation (Nelson and Ellenberg 1990), even though they may adversely influence the prognosis with regard to later afebrile seizures. Some delay in passing early milestones may be slightly more frequent than in the general population (Wallace 1988). The only predictors of febrile convulsions are a fever >38°C and a family history of febrile seizures (Bethune et al. 1993; Berg et al. 1995).

The incidence of seizures after diphtheria-pertussis-tetanus vaccination has decreased with the abandonment of whole-cell vaccines in favour of acellular vaccines which are less reactogenic. Febrile seizures that occur within 48 hours of immunisation are not clinically distinct from febrile seizures due to other causes. However, patients with Dravet syndrome are particularly vulnerable to immunisation-induced febrile seizures which are described in up to one-third of cases (Cendes and Sanker 2012). Vaccination-induced seizures in patients with Dravet syndrome do not significantly affect the subsequent clinical or cognitive evolution (Zamponi et al. 2013).

**CLINICAL AND EEG FEATURES OF FEBRILE CONVULSIONS**

The great majority of febrile convulsions are brief, bilateral clonic or tonic–clonic seizures. Unilateral seizures occur in about 4% of patients. These are often prolonged seizures lasting 30 minutes or more (Nelson and Ellenberg 1981). Seizures lasting more than 15 minutes, unilateral seizures, and those followed by a Todd paralysis are termed complex febrile convulsions and have a higher risk (up to 50%) of being followed by epilepsy. However, most cases of epilepsy subsequent to febrile convulsions occur after brief (so-called simple) febrile convulsions, just because these are overwhelmingly frequent and despite their lower attendant risk of epilepsy (about 1%).

Febrile convulsions lasting 30 minutes or more are one type of status epilepticus and may cause sequelae if untreated (Aicardi and Chevrie 1976; Viani et al. 1987; Phillips and Shanahan 1989). These include the hemiconvulsion–hemiplegia–epilepsy syndrome (Arzimanoglou and Dravet...
The role of long-lasting febrile convulsions in the genesis of focal epilepsy, especially the syndrome of mesial temporal epilepsy with hippocampal sclerosis, remains disputed. MRI studies have shown evidence of acute swelling of the hippocampus in the days following a long febrile convulsion (VanLandingham et al. 1998; Scott et al. 2003). The later development of hippocampal atrophy and sclerosis in patients with intractable temporal lobe epilepsy and a history of prolonged febrile seizures (Kuks et al. 1993; Holthausen 1994; Harvey et al. 1995; Cendes et al. 2005) are strong arguments in favour of a causal relationship in many cases. Thus, vigorous treatment of febrile status is imperative, as shown by the persistence of sequelae in areas where emergency treatment is not available and febrile seizures are allowed to go untreated for hours.

Compared to children with simple febrile seizures, febrile status epilepticus is associated with younger age, lower temperature, longer duration of recognised temperature before the seizure, female sex, structural temporal lobe abnormality and first-degree family members with a history of febrile seizures (Hesdorffer et al. 2013). These diverse features suggest that children with febrile status epilepticus are predisposed by a combination of factors.

Most cases of prolonged febrile convulsions occur during the first 18 months of life and especially before the age of 12 or 13 months. After 2 years of age, the risk of status epilepticus decreases (Aicardi and Chevrie 1983; Arzimanoglou et al. 2004). The role of developmental malformations in the aetiology of temporal lobe seizures following febrile convulsions may also be considered, either as explaining the whole sequence of the febrile seizures that are followed by unprovoked seizures or as a factor determining the localisation and severity of the febrile convulsions. The latter would then constitute a ‘second hit’ in the full sequence leading to hippocampal sclerosis.

EEG tracings recorded within a week of a febrile convolution are abnormally slow for a few days in approximately one-third of patients. Epileptiform discharges occur in one-third of children with febrile convulsions followed prospectively whether in the form of rolandic spike foci or bilateral spike–wave bursts (Kajitani et al. 1981; Sofijanov et al. 1992). However, the real figures may be lower because hypnagogic bursts, frequent in this age bracket, may be misdiagnosed as actual paroxysms. Such abnormalities are poorly correlated with the later occurrence of epilepsy (Sofijanov et al. 1992). In particular, they are exceptional in children below 18 months of age who are particularly at risk of recurrence of the development of afebrile seizures (Viani et al. 1987), whereas they occur in up to 50% of 4-year-olds who are at much lower risk. Therefore, EEG recording is not indicated in the management of febrile convulsions.

The clinical features of febrile status epilepticus are being studied in greater detail in a large prospective multicentre prospective study examining the consequences of prolonged febrile seizures lasting at least 30 minutes in children ages 1 month to 5 years (FEBSTAT) (Shinnar et al. 2008; Hesdorffer et al. 2012). In this population, febrile status epilepticus was often the initial presentation and was continuous in 52% and behaviourally intermittent in 48%. Mean febrile seizure duration was 68 minutes (range 1–24 hours) with 24% of affected individuals experiencing seizures lasting more than 2 hours. Almost all cases (99%) were convulsive and were focal in approximately half. Somewhat disconcerting was the recognition that a third of all cases went unrencognised in emergency departments.

EEGs in the FEBSTAT cohort recorded within 72 hours of the status revealed high rates of focal slowing or background attenuation. These EEG changes were highly correlated with subsequent MRI revealing hippocampal damage (Nordli et al. 2012). This association suggests that the EEG abnormalities that appear early in the course of febrile status epilepticus may serve as markers of structural alteration.

The FEBSTAT trial and two affiliated studies further examined a cohort of 226 children with febrile status epilepticus to determine its role in the evolution of hippocampal injury (Lewis et al. 2013). All participants were studied with acute MRI and follow-up MRI at 1 year. Acute hippocampal T2 signal hyperintensity changes that were maximal in Sommer’s sector were associated with increased hippocampal volume indicative of oedema in 22 children. Follow-up MRI in 14 of the 22 children with acute changes revealed hippocampal sclerosis in ten and reduced hippocampal volume in 12. In contrast, only one of 116 children without acute changes evidenced abnormal T2 signal. Even participants with normal acute studies were prone to smaller hippocampal volumes and reduced hippocampal growth. This would suggest a subtler injury that is MRI negative (Lewis et al. 2014).

Given the association of febrile seizures and later hippocampal sclerosis, and the relationship of the SCN1A mutation to febrile seizures, Kasperaviciute et al. (2013) performed a genome-wide association study of a large cohort of individuals with mesial temporal lobe epilepsy and hippocampal sclerosis with and without a history of febrile seizures. Meta-analysis revealed a significant genetic association of mesial temporal lobe epilepsy and hippocampal sclerosis with febrile seizures at the sodium channel gene cluster on chromosome 2q24.3, within an intron of the SCN1A gene. These findings provide further understanding of a biological predisposition in this clinical setting.

Histopathological studies of temporal lobe tissue removed at epilepsy surgery reveal an unexpectedly high incidence of the HHV6B virus replication in hippocampal astrocytes (Theodore et al. 2008). This agent is commonly associated with roseola infantum but may reactivate to cause limbic encephalitis in immunologically compromised patients. As HHV6B viral infection could play an important role linking early viral infection, febrile status epilepticus and hippocampal sclerosis, serum has recently been screened for this agent in patients with febrile status epilepticus. The HHV6B virus was identified in one-third of specimens (Epstein et al. 2012). In contrast,
HHV7 virus occurs much less commonly (Epstein et al. 2012). No child diagnosed with herpesvirus viremia had evidence of cerebrospinal fluid (CSF) involvement.

**Differential diagnosis in febrile convulsions**

The differential diagnosis of febrile convulsions includes primarily seizures with infections of the CNS (meningitis and encephalitis). In CNS infections, there is almost always an abnormal CSF. Green et al. (1993) found that none of 115 children with convulsions associated with meningitis had occult disease. However, such cases are known to occur (Heijbel et al. 1980), so lumbar puncture is advised in children under age 18 months and especially under 6 months of age. Lumbar puncture is also indicated in children with long-lasting or otherwise atypical convulsions and in those who fail to recover full consciousness promptly.

Herpes encephalitis in infants often manifests itself initially with febrile focal seizures and may pose an important clinical problem. Puchhammer-Stöckl et al. (1993) reported on 257 patients with suspected herpes simplex virus encephalitis prospectively analysed by herpes simplex virus polymerase chain reaction (PCR). The PCR indicated herpes simplex virus encephalitis in nine serologically proven cases and in 14 additional patients. Increased PCR signals were observed together with more severe neurological symptoms ($P < 0.01$) and within the first days of acyclovir treatment ($P < 0.05$). In such cases, MRI can be of considerable value by showing signal alterations in a localised or multifocal distribution.

Differentiating acute convulsive encephalopathies from febrile seizures may be difficult if the CSF is normal. Indeed, the distinction is sometimes made only a posteriori, cases with sequelae not being regarded as febrile convulsions. However, cases of febrile convulsions with sequelae do exist and are important in assessing the prognosis of febrile seizures. Likewise, it is very difficult to separate febrile seizures from ‘true’ epileptic seizures precipitated by fever as there is a large overlap between these categories. Dravet syndrome starting with prolonged unilateral febrile seizures may be difficult to diagnose early. Repetition of long-lasting seizures within a short period (<2 months) is suggestive. Non-epileptic paroxysmal events are frequent in febrile children and include febrile syncope (‘anoxic seizures’) (Stephenson 1990); febrile delirium and rigors can also be mistaken for febrile convulsions.

**Prognosis of febrile convulsions**

The prognosis of febrile convulsions is generally extremely favourable. Approximately 60–70% of children have only one episode of febrile convulsions and most of the remaining will have two or three seizures. Only 9% of patients experience more than three episodes. Three-quarters of the recurrences take place during the year following the first seizure, and the risk of severe recurrence is quite low (Nelson and Ellenberg 1981; Annegers et al. 1990; Van Esch et al. 1996). The risk of recurrence is greater in children with seizures in the first 2 hours of fever or with a temperature below 40°C; those with a family history of febrile or afebrile seizures, children under 1 year of age and patients with two or more episodes. Complex febrile seizures are also a predictor of a higher risk of recurrence (Offringa et al. 1994; Baram and Shinnar 2002).

The risk of developing afebrile seizures is approximately 2–5%. It is lower in children with simple seizures after age 1 year but increases at a younger age. The presence of previous developmental or neurological abnormality, a family history of epilepsy, and complex febrile convulsions (Verity et al. 1993) all increase the risk of developing afebrile seizures, which reaches up to 50% when all three factors are present (Annegers et al. 1990).

The majority of epilepsies following febrile convulsions are nonlesional generalised epilepsies with tonic-clonic seizures, often with only a few seizures (Wallace 1991; Camfield et al. 1994). Such cases mainly follow brief, uncomplicated febrile convulsions (Aicardi and Chevrie 1976) and are relatively common. Afebrile seizures are mostly infrequent and generally tend to disappear by age 9–10 years (Arzimanoglou et al. 2004).

Focal epilepsy may occur after long-lasting unilateral seizures (Aicardi and Chevrie 1976, 1983), although their exact frequency is unclear. Whether afebrile seizures are a direct consequence of febrile convulsions is debated, but the fact that such seizures are observed following febrile convulsions is well established.

The neurodevelopmental prognosis of febrile convulsions is excellent, except in patients who develop epilepsy, some of whom develop learning difficulties. This illustrates the tendency of complications to occur in association and is often the case with accidental prolongation of an episode of febrile convulsions. Some affected children may have had a previous subclinical brain lesion before the febrile seizure with the result that it was long-lasting and localised. This is in agreement with the relatively high incidence of abnormal pre- and perinatal history found in several studies (Chevrie and Aicardi 1975; Wallace 1988).

**Treatment of febrile convulsions**

Brief febrile convulsions do not require treatment apart from the causative febrile illness (Baram and Shinnar 2002). Simple measures such as removal of excess blankets and physical cooling are usually recommended. However, there is no evidence that antipyretic agents are effective in the prevention of febrile convulsions (Uhari et al. 1995). Hospitalisation is unnecessary for uncomplicated febrile convulsions if adequate surveillance is possible. In case of doubt, a 12-hour hospitalisation is sufficient. Long-lasting episodes should be treated vigorously (see Table 16.14 in the section on treatment of status epilepticus) to avoid the later emergence of epilepsy and its sequelae, especially for seizures before age 1 year. Parents and caregivers should be instructed on how to rapidly administer rectal diazepam (at a dose of 0.5–1mg/kg) or buccal or nasal midazolam for acute febrile episodes lasting more...
than 2–3 minutes (McIntyre et al. 2005; Wait et al. 2013; Cross et al. 2013).

Continuous prophylactic treatment of recurrences is not generally advised (Consensus Developmental Panel 1980) but may be indicated when factors of high risk are present. Our own practice is to treat systematically infants below 1 year of age; treatment for patients with complex febrile seizures may be indicated, although there is no proof that it prevents the occurrence of later epilepsy (Nelson and Ellenberg 1981; Shinnar and Berg 1996). The balance of risks and advantages is generally against prophylactic therapy. The American Academy of Pediatrics Practice Parameter Committee reached a similar conclusion and stated that the potential toxicity associated with antiepileptic therapy outweighs the relatively minor risks associated with simple febrile seizures. Thus, long-term treatment is not recommended (Baumann and Duffner 2000). Phenobarbital (30–40mg/kg/day) that reaches a blood level of around 15µg/mL is reasonably safe, although concern has been expressed about the effects of the drug on IQ levels (Farwell et al. 1990) and for this reason it has largely been abandoned. Sodium valproate reduces the recurrence rate to a similar extent (Wallace 1988), provided an underlying metabolic disorder is excluded. More recently developed AEDs, particularly levetiracetam for which PK data in very young children is available (Arzimanoglou et al. 2016b), are reasonable alternatives.

Intermittent prophylaxis with oral diazepam was reported effective provided large enough doses are used (0.5mg/kg t.i.d.) (Aubet et al. 1990; Rosman et al. 1993; Knudsen 1996). However, efficacy is limited by the early occurrence of seizures, which may be the first symptom of fever – as was the case in 25% of patients in the series reported by Wolf et al. (1977). Knudsen et al. (1996) reported on a cohort of 289 children with febrile convulsions who had been randomised in early childhood to either intermittent prophylaxis (diazepam at fever) or no prophylaxis (diazepam at seizures) and followed up 12 years later. Children with simple and complex febrile convulsions had the same benign outcome. The long-term prognosis in terms of subsequent epilepsy and neurological, motor, intellectual, cognitive and scholastic ability was not influenced by the type of treatment applied in early childhood. They concluded that it was ‘as good to interrupt as to prevent’ a febrile seizure and that prophylactic treatment at the time of fever should be reserved for special cases. Intermittent treatment of fever with acetaminophen alone (Bethune et al. 1993) or combined with low-dose diazepam (Uhari et al. 1995) is not effective. A larger availability of easier to administer rescue formulations, such as buccal or nasal midazolam, will further reduce the indications for the prescription of intermittent prophylaxis.

Recent recommendations for treatment of febrile seizures by the Italian League Against Epilepsy have re-affirmed these principles (Capovilla et al. 2009). Prophylactic therapy was not recommended for simple febrile seizures while rectal or buccal benzodiazepines are indicated for acute seizure termination.

Convulsive febrile status epilepticus is a medical emergency. Treatment should be offered within 2 minutes of seizure onset (or earlier) with either intravenous diazepam or lorazepam if possible (Neville et al. 2007). Home treatment with rectal diazepam or buccal midazolam are also effective in the majority of cases. More than two doses of benzodiazepines or the co-administration of barbiturates should be discouraged as there is a significant possibility of respiratory depression.

**Generalised Epilepsy with Febrile Seizures Plus**

The term ‘generalised epilepsy with febrile seizures plus’ was first used by Scheffer and Berkovic (1997) to describe ‘a genetic disorder with heterogeneous clinical phenotypes’. The description was based on the recognition that in one large Anglo-Australian extended family, febrile seizures, often of unusual duration or severity, and afebrile generalised seizures of various types appeared to be transmitted as a dominant genetic trait. Simple febrile seizures constituted the most common manifestation. However, they often occurred beyond the usual upper limit of 6 years, and the term ‘febrile seizures plus’ was proposed for children with febrile seizures persisting after the age of 6 years.

Afebrile seizures, mainly generalised tonic–clonic ones, but in some cases, myoclonic seizures myoclonic–astatic epilepsy or even episodes of status epilepticus occurred in some pedigree members. The pattern of inheritance was autosomal dominant. Although GEFS+ is named after the occurrence of generalised tonic–clonic seizures, these are not the only type of seizures that are observed. Indeed, in some individual cases, such seizures may be absent altogether. More often they are associated with other seizure types. The very term of ‘syndrome’ may not be appropriate to designate the condition as it is not characterised by the ‘non-fortuitous association of signs and symptoms in one individual patient but by its genetic nature indicated by the familial occurrence and by the demonstration of the same genes in affected persons of GEFS+ families in some cases’ (Arzimanoglou 2007).

Other authors reported that patients within the GEFS+ spectrum may present with focal seizures like temporal lobe epilepsy (Abou-Khalil et al. 2001) that is variably associated with hippocampal sclerosis. The fact that GEFS+ is linked to mutations in genes coding for sodium channels and GABA-A receptors suggested that this ‘genetic syndrome’ belongs to the ‘channelopathies’. The mechanism for the phenotypic variability in GEFS+ families is uncertain.

A locus for the GEFS+ spectrum was mapped to chromosome 19q13, where the voltage-gated sodium channel 1 subunit gene (**SCN1B**) had been assigned. A second mutation in **SCN1A**, which encodes for the alpha-1 subunit of the same sodium channel, with linkage to chromosome 2q24–33, was found in patients with a similar clinical picture. Claes et al. (2001) found different mutations of this gene in seven children with Dravet syndrome (see Dravet Syndrome section). The GABA-A receptor gamma-2 subunit gene, GABRG2
Febrile Infection-Related Epilepsy Syndrome (FIRES)

Febrile infection-related epilepsy syndrome (FIRES) was described in typically developing children with a catastrophic onset illness mimicking infectious encephalitis. Affected patients are typically school-age and experience a nonspecific febrile illness followed by altered cognitive status and seizures that rapidly evolve to focal status epilepticus that is refractory to AEDs and immunotherapy, and requires management in an intensive care setting (Kramer et al. 2011). FIRES has been reported under a variety of descriptive titles including devastating encephalopathy in school-age children (DESC) (Mikaeloff et al. 2006), acute encephalitis with refractory repetitive partial seizures (AERRPS) (Sakuma et al. 2010) and fever-induced epileptic encephalopathy of school-age children (Nabbout et al. 2011).

The occurrence of fever and mild CSF pleocytosis in some patients has suggested an infectious or immune-mediated aetiology but no organism or autoimmune dysregulation has been identified. Histological examination of biopsied or autopsied brain tissue has not revealed any inflammatory changes. A protracted intensive care course is the rule. Attempts to control the status epilepticus are often unsuccessful despite heroic measures with intravenous and anaesthetic anti-seizure agents. Gradually, the clinical course evolves into a state of chronic epilepsy. Frequent medically refractory seizures may present later with recurrence of seizures or an increase in frequency.

Most epilepsy syndromes of later childhood and adolescence are unassociated with gross brain damage, and genetic factors probably play a prominent role. As a result, affected children are usually normal both cognitively and neurologically, and prognosis is generally better than for early-onset epilepsies where brain lesions are common.

SEIZURES AND SYNDROMES OF LATE CHILDHOOD AND ADOLESCENCE

Several of the epilepsy syndromes of infants and young children may persist or have their onset later in life, and there is no definitive separation between age groups. They can manifest with generalised (absences, myoclonic, tonic–clonic seizures) or focal seizures. Focal non-idiopathic (structural) epilepsies having presented earlier in life with just a few, easily controlled seizures may present later with recurrence of seizures or an increase in frequency.

SYNDROMES OF LATE CHILDHOOD AND ADOLESCENCE WITH PREDOMINANTLY TYPICAL ABSCENCES

The International Classification recognises two varieties of absences: typical and atypical. To avoid confusion when discussing seizure phenomenology, Lüders et al. (1999) suggested the term dialeptic seizures, underscoring the fact that a further distinction between typical and atypical absences can be made only when EEG findings or a more precise syndromic diagnosis become available. The term, although correct from a semantic point of view, was not really adopted from the epileptological community.

Typical absences are a well-defined seizure type with a characteristic EEG correlate. They are characterised clinically by the sudden suppression or marked decrease of consciousness, with abolition of awareness, responsiveness and memory function (Hirsch and Panayiotopoulos 2005). They can be simple or complex. Simple typical absences last 5–15 seconds in 90% of cases (Penry et al. 1975) and usually do not involve motor phenomena, except for possible mild jerking of eyelids and minor changes in muscle tone. The onset and termination of a typical absence are relatively abrupt: this is of value to differentiate absences from focal seizures with alteration of consciousness and minimal motor symptoms. The
same also applies to the lack of a postictal phase of impaired awareness and/or fatigue (Penry et al. 1975). In complex typical absences, more marked motor components (increased or decreased muscle tone), simple automatisms (Penry et al. 1975) and autonomic phenomena accompany the loss of consciousness and the duration of the attack is often longer. As discussed below, the degree of consciousness impairment is variable depending on the epilepsy syndrome of which the typical absences are a part (Panayiotopoulos et al. 1989).

The EEG in typical absences, whether simple or complex, shows rhythmical bursts of spike–wave complexes at a rhythm of 2.5–3.5Hz that are bilateral, synchronous and symmetrical with abrupt onset and termination (Fig. 16.9). Less rhythmical discharges may occur, especially during sleep, and some degree of asymmetry is present in 9% of cases (Loiseau et al. 2002). EEG variants are observed in some absence syndromes (Panayiotopoulos et al. 1989; Hirsch and Panayiotopoulos 2005). The interictal records are often normal, but brief bursts of irregular spike–wave complexes are seen in 30% of patients. Posterior 3Hz slow waves occur in 10–20% of children with typical absences.

Hyperventilation is highly effective in precipitating typical absences and can be performed safely in the clinic in patients who do not manifest signs of cerebrovascular disorder (to be avoided in the presence of moyamoya disease). In an untreated child, a negative test makes the diagnosis of absences unlikely. About 10–20% of children with absences respond to light stimulation which is a risk factor for ‘grand mal’ seizures.

Absences should be distinguished from inattention and day-dreaming, tics, abnormal head movements and stereotypes. Distinction from focal seizures with impaired awareness may sometimes be difficult, although typical absences are usually much more frequent (the term ‘pykno-lepsy’, signifying ‘dense in frequency’ was also used). The brief duration of episodes, their frequent repetition and the lack of a postictal phase are all important features, but an EEG with ictal recording is necessary for a definitive diagnosis. Differentiation from atypical absences rests on the different history, often with other seizure types besides absences and the EEG findings. Atypical absences occur mainly in LGS and some forms of polymorphic epilepsy. Absences due to frontal lobe damage result from post-traumatic atrophy or tumours (Ferrie et al. 1995).

The occurrence of typical absences as the predominant or exclusive type of seizure is the hallmark of absence epilepsy. Several syndromes of absence epilepsy are recognised. These include absence epilepsy of childhood, absence epilepsy of adolescence, absences in juvenile myoclonic epilepsy, myoclonic or clonic absences and some rarer syndromes (Panayiotopoulos 1998, 2002).

**Childhood Absence Epilepsy (CAE)**

Childhood absence epilepsy (CAE), also called pykno-lepsy or (incorrectly) petit mal, has its onset between the ages of 3 and 8 years, although rare cases are described as early as the first year of life (Aicardi 1995; Chaix et al. 2003). It is more common in girls than in boys. The absences occur many times daily and constitute the first manifestation of epilepsy, although febrile convulsions may have occurred in infancy. Affected children are normal between episodes of the interictal EEG, is also normal although brief bursts of spike–wave complexes without clinical absence may be recorded. The absences do not include prominent clonic or atonic
phemonena but simple automatisms and complex absences are common (Loiseau and Duché 1995; Loiseau et al. 2002). The loss of awareness is marked, and the eyes open during the discharge (Panayiotopoulos 1994b, 1998). In typical cases neuroimaging is not indicated as there is no appreciable brain pathology; a family history of seizures is relatively frequent. The occurrence of several cases of absence epilepsy in the same lineage is not rare (Loiseau and Duché 1995) and polygenic inheritance appears likely.

Treatment with sodium valproate, ethosuximide or lamotrigine is usually effective (Arzimanoglou et al. 2004; Hirsch and Panayiotopoulos 2005). Glauser and colleagues have undertaken an important multicentre, randomised, double-blind trial in 453 children with newly diagnosed childhood absence epilepsy (Glauser et al. 2010). Lamotrigine, the only second-generation drug approved for the treatment of absence seizures, was included for comparison. At the final assessment after 16–20 weeks of treatment (children eligible for a final dose increase at week 16 were followed up for 4 additional weeks), valproate and ethosuximide were similarly effective, but valproate caused greater attentional dysfunction as determined by the Conners’ continuous performance test than the other drugs. Because of this association and because lamotrigine monotherapy had a lower success rate (29% free from treatment failure) than ethosuximide (53%) and valproate (58%), the authors concluded that ‘ethosuximide is the optimal initial empirical monotherapy for childhood absence epilepsy’.

When drugs have equivalent efficacy, comparative side effect profiles become paramount in making treatment decisions, which is why the results of the Glauser et al. study (2010) are likely to affect current practice. In their study, less than 15% of children randomly assigned to ethosuximide or valproate had treatment failure because of poor seizure control, but intolerable adverse effects occurred in 24% of children assigned to each of these drugs. Thus, the only reason for preferring ethosuximide to valproate is the reported greater occurrence of neuropsychological impairment with valproate. Attentional difficulties occurred at baseline with a higher frequency in the valproate cohort (42%) than in the ethosuximide (34%) or lamotrigine (30%) cohorts. Undoubtedly this very well-designed study has many merits and long-term follow-up of the cohort is ongoing. When considering the results, the reader should, however, also take into account that in children with uncontrolled seizures, drug dose should be increased according to tolerability up to a maximum dose, which was 60mg/kg per day for valproate (Arzimanoglou et al. 2010). In several European countries, the highest recommended dose of valproate is 30mg/kg per day, and it is possible that a lower ceiling dose might improve tolerability without compromising efficacy. Older children who are approaching an age consistent with juvenile absence epilepsy (see Juvenile Absence Epilepsy section) have an increased risk of generalised tonic–clonic seizures that are suppressed by valproate but not ethosuximide.

For refractory cases, the combination of two drugs may be effective. In our practice, we often administer lamotrigine with low-dose valproate. In some resistant cases, benzodiazepines (especially clobazam) may control otherwise intractable seizures. Similar results were reported with sulthiame (Gorman and Shahwan 2016). Typical absence seizures do not respond to many AEDs including carbamazepine, oxcarbazepine, vigabatrin, gabapentin and phenytoin, which in some cases may increase seizure frequency or facilitate the occurrence of myoclonias.

The outlook of CAE is favourable. However, absences can persist into adulthood in a small proportion of cases, and generalised convulsions develop in about 10–30% of patients followed into adulthood although they are infrequent and easily treatable (Loiseau et al. 1983). Wirrell et al. (1996) showed that only 65% of children presenting with CAE had remission of their epilepsy. Forty-four per cent of those without remission had developed juvenile myoclonic epilepsy (JME). At the time of diagnosis, remission is difficult to predict accurately in most patients. Development of generalised tonic–clonic or myoclonic seizures during AED treatment was ominous, predicting both lack of remission of CAE and progression to JME. Trinka et al. (2004) reported a similar experience. The educational achievements are often less than optimal. The socio-professional outlook for CAE is less favourable than that of rolandic epilepsy, and affected individuals often fare less well than their cognitive level would normally allow (Loiseau et al. 1983).

Juvenile Absence Epilepsy (JAE)

Juvenile absence epilepsy (JAE) occurs in patients presenting beyond the age of 9–10 years, although the borderline between childhood and juvenile types is incompletely demarcated. Absences in adolescents are usually less frequent than in children and often cluster in the hour following awakening. Loss of consciousness is less complete than in childhood absence epilepsy (Panayiotopoulos 1994b, 1998), and in some cases the absences are hardly detectable even by the patient.

Other types of seizures, especially generalised tonic–clonic seizures, occur in 90% of cases, and myoclonic seizures may also be present. In the latter cases the absences may be especially mild and often produce only subclinical discharges. The EEG of juvenile absence is either identical to childhood absence epilepsy (Panayiotopoulos 1994b, 1998), and in some cases the absences are hardly detectable even by the patient.

Typical absences also occur in juvenile myoclonic epilepsy where they may precede the appearance of other seizure types (Martinez-Juarez et al. 2006). Such cases might be a subgroup of JME and might be responsible for some cases of absences that evolve into medically resistant adult epilepsy (Panayiotopoulos 2002).

Juvenile absences, generalised tonic–clonic seizures on awakening and JME, often present as a triad of idiopathic (genetic) generalised epilepsy of adolescence. The associated tonic–clonic seizures and sometimes absences often persist into adulthood.
Treatment choices are similar to CAE. However, ethosuximide is unsuitable as a monotherapy as it may control absence seizures but not convulsions. Treatment must be prolonged particularly for female patients. Issues related to contraception and/or future pregnancy must be considered when first choosing antiepileptic drug therapy (see section AEDs and Pregnancy Related Issues).

Other Syndromes Featuring Typical Absences

The rare syndrome of **epilepsy with myoclonic absences** (clonic absences) is characterised by a specific seizure type, the **myoclonic absences** (Bureau and Tassinari 2005). Clinically, the intensity of the clonic jerking that affects the upper and often the lower limbs is distinctive. The EEG expression is non-specific with bilateral rhythmic spike–wave discharge at 3Hz similar to cases of typical absences. Rare onset occurs during the first year of life but mean age at onset is 7 years; the course is variable. Some cases develop intellectual disability and may evolve to LGS while others respond promptly to treatment and have a benign course (Manonmani and Wallace 1994; Bureau and Tassinari 2005). Some children develop tonic seizures. The classic treatment combines sodium valproate with ethosuximide or lamotrigine. Benzodiazepines may also be useful.

Other less well-defined syndromes include cases of absences preceded by generalised tonic–clonic seizures other than absences (Dieterich et al. 1985) that generally have an unfavourable outcome, **eyelid myoclonia with absences** (Jeavons syndrome) which is essentially a form of myoclonic epilepsy (see Juvenile Myoclonic Epilepsy section), and **perioral myoclonia with absences**, which may prove drug resistant. The individualisation of some of these syndromes is unclear (Arzimanoglou et al. 2004). Very slight absences, often unreocgnised even by the patient and sometimes revealed only by associated rare tonic–clonic seizures, have been termed **phantom absences** (Panayiotopoulos 2002).

Absences associated with brain injury are rare (Ferrie et al. 1995) but may occur with either diffuse lesions or focal damage, especially to the mediobasal frontal lobe. A focal component (clinical and/or EEG) may be present. In most cases the association is probably coincidental.

The genetics of epilepsies featuring typical absences (see Table 16.2) are imperfectly understood. Typical CAE appears to be genetically unrelated to JME, and linkage to chromosome 6p has been excluded. Photosensitive cases seem to be genetically distinct, often with a dominant inheritance, and some may be genetically related to JME (Bianchi et al. 1995). Rare cases of absences linked to definite mutations are on record (Hirose et al. 2005; Ito et al. 2005).

**SYNDROMES OF LATE CHILDHOOD AND ADOLESCENCE WITH PROMINIDENTLY GENERALISED TONIC-CLONIC SEIZURES**

Generalised tonic–clonic seizures (or bilateral tonic–clonic seizures) may be generalised from the start and are often a manifestation of idiopathic (genetic) epilepsy. They may also represent the secondary generalisation of a focal seizure that is traditionally termed the ‘aura’ of the generalised attack. These two types may be difficult to separate clinically, although their aetiological significance is different (Arzimanoglou et al. 2004; Hirsch et al. 2006a).

**Primary generalised tonic–clonic seizures** comprise a stereotyped succession of events, beginning with a tonic contraction of the entire musculature with respiratory blockade resulting in cyanosis and loss of consciousness. After 10–30 seconds, the tonic phase gives way to clonic jerks that progressively slow and become increasingly violent. Muscle relaxation occurs after 30–60 seconds. The patient remains unconscious for variable durations. Tongue biting and urinary or, rarely, double incontinence are frequent but nonspecific as they also occur with nonepileptic seizures (Stephenson 1990). Generalised tonic–clonic seizures are characterised by the succession of a fast (≥10Hz) rhythm of increasing amplitude that becomes fragmented during the clonic phase, evolving to single spike–wave complexes. An electrodecremental response follows the clonic phase but is rapidly replaced by slow waves that progressively decrease merges with interictal tracing. The EEG may show generalised spike–wave complexes, sometimes with a positive response to photic stimulation. Lateralisations manifestations including versive movement or circling may occur in patients with typical bilateral paroxysms (Gastaut et al. 1986; Lancman et al. 1994). Although relatively straightforward to diagnose, some idiopathic generalised seizures exhibit focal features that create diagnostic problems (Ferrie 2005) and some symptomatic epilepsies (Oguni 2005).

Secondarily generalised tonic–clonic seizures present in two ways (Theodore et al. 1994). In some cases, the initial focal seizure manifests clinically with localised motor, sensory or other phenomena. In others, the seizure is generalised at onset while the ictal EEG reveals an initial, clinically silent focal discharge. When ictal records are unavailable, the presence of a stable interictal spike focus – present in 20–40% of patients with tonic–clonic seizures (Arzimanoglou et al. 2004) – provides indirect evidence for secondarily generalised seizures. Such seizures are usually the expression of a localised brain lesion but may also occur with nonlesional epilepsies.

Syndromes with secondarily generalised seizures will be discussed in detail in the section on focal epilepsies.

Atypical tonic–clonic seizures are very common in childhood: the clonic phase may be extremely brief and EEG activity is not always synchronous or symmetrical. In some children, the tonic phase is too brief to be noted. Generalised tonic–clonic seizures occur in several epilepsy syndromes and are, therefore, non-diagnostic. Indeed, when they occur in association with other seizures in the same patient, the latter are considered more characteristic. For example, in this age range, their association of typical absences suggests the diagnosis of juvenile absence epilepsy (see Juvenile Absence Epilepsy section), while the presence of myoclonic jerks suggests juvenile myoclonic epilepsy (see Juvenile Myoclonic Epilepsy section).
Epilepsy with Grand Mal Seizures on Awakening or Epilepsy with Generalized Tonic-Clonic Seizures Alone

Epilepsies with exclusively or predominantly generalised tonic–clonic seizures have also been classified according to their relationship to the sleep–waking cycle: awakening grand mal; grand mal of sleep; and diffuse (or of random distribution) grand mal (Janz 1994; Wolf 2002; Genton et al. 2005; Fernández and Salas-Puig 2007). The only relatively well-defined syndrome in this category is grand mal on awakening, considered as a form of idiopathic generalised epilepsy. However, the diagnosis of this condition is difficult as a strict relation to awakening is necessary for the diagnosis, and the number of seizures necessary for diagnosis is arbitrary. Janz (1994) stated that the diagnosis should be accepted only if 90% of seizures occur within 30 minutes of awakening, whereas Wolf (2002) requires that the clear majority of seizures must occur in the first 2 hours after awakening. Andermann and Berkovic (2001) suggest that the three syndromes of awakening grand mal, juvenile myoclonic epilepsy and juvenile absences are variants of a broader epilepsy syndrome termed primary generalised epilepsy. The term ‘epilepsy with generalised tonic–clonic seizures alone’ was the one priviledged in the latest ILAE Classification (Scheffer et al. 2017).

Triggering factors include sleep deprivation, photic stimulation, and excessive alcohol intake, and counselling is therefore important. Pharmacological sensitivity is probably similar to other idiopathic generalised epilepsies (valproate, lamotrigine, topiramate or levetiracetam), but controlled studies are lacking. Duration of treatment is unknown and should be decided on an individual basis.

SYNDROMES OF LATE CHILDHOOD AND ADOLESCENCE WITH PREDOMINANTLY MYOCLOUS SEIZURES

In some epilepsies of late childhood and adolescence, myoclonias constitute a predominant, if not exclusive, proportion of the seizures. The epilepsies characterised by marked myoclonic phenomena in this age range are, in most cases, idiopathic in origin. A strong genetic predisposition to convulsive disorders is very common (Arzimanoglou et al. 2004). A phenomenon that is more typical of older children and adolescents is a succession of myoclonic jerks often culminating in a generalised tonic–clonic seizure (clonic–tonic–clonic seizure). Myoclonic seizures in this setting differ in outlook and therapy from that observed in Lennox–Gastaut or Dravet syndrome (discussed in the Seizures and Syndromes of Infancy and Early Childhood section). Properly recognising the different types of seizures is important and involves not only detailed history but also video-EEG. The precise determination of the other seizure types that often accompany myoclonic seizures is also important, as the associated seizures are critical for making the most appropriate diagnosis and for classifying the myoclonic epilepsies.

Epilepsy syndromes with prominent myoclonus are divided into four main types:

1. Absence seizures associated with myoclonus (epilepsy with myoclonic absences and eyelid myoclonia with absences; also see Other Syndromes Featuring Typical Absences section);
2. Myoclonic seizures induced by intermittent photic stimulation (see Stimulus-Sensitive or Reflex Epilepsies section);
3. Adolescent-onset ‘grand mal’ seizures as the main seizure type with associated absence seizures (i.e. juvenile myoclonic epilepsy, discussed in the Juvenile Myoclonic Epilepsy section);
4. Rhythmic distal myoclonus with onset between late childhood into adulthood; these are mostly familial, with prominent generalised jerks and tonic–clonic and focal seizures in some patients.

Duron et al. (2005) have reviewed the frequency of different seizure types in generalised epilepsy syndromes, their age dependency and the temporal profile of seizures. Progressive myoclonic epilepsies (PME) are also treated in this section, with respect to age range at onset.

Juvenile Myoclonic Epilepsy (JME)

Juvenile myoclonic epilepsy (JME) (also referred to as myoclonic epilepsy of adolescence or Janz syndrome) is the most frequent and well-defined idiopathic generalised epilepsy syndrome. Onset occurs between 12 and 18 years (Delgado-Escueta and Enrile-Bacsal 1984; Janz 1989) but may occur outside this age range. The condition has been termed ‘myoclonic petit mal’ or ‘impulsive petit mal’, a term that is confusing as JME clearly differs from absence epilepsy. It occurs in 5–11% of adolescents with epilepsy. The myoclonic jerks typically involve the shoulders and arms, and uncommonly the lower extremities. They may be asymmetrical or even unilateral (Genton et al. 1994; Janz 1994). Consciousness is usually preserved, but the involuntary movements often result in the patient throwing whatever is held (French authors term this ‘le syndrome de la soucoupe volante’, i.e. the flying saucer syndrome).

The jerks occur mainly after awakening as single shocks or serial jerks that rarely produce myoclonic status. Ninety percent of patients experience associated generalised tonic–clonic seizures. The latter may sometimes supervene following a series of jerks, a sequence referred to as a clonic–tonic–clonic seizure. Fifteen to 30% of patients also have absence seizures. The complex relationship between the various idiopathic (genetic) generalised epilepsies is discussed by Thomas et al. (2005).

The typical ictal EEG consists of a burst of high frequency spikes followed by one or a series of slow waves (Figs 16.10 and 16.11). Similar polyspike–wave complexes may occur interictally. Focal EEG features occur in up to 20% of cases (Panayiotopoulos 1994a). Sleep deprivation and photic stimulation can trigger seizures.
About 80% of patients respond well to sodium valproate therapy, but treatment should be long-standing, probably indefinitely. In women with JME, future pregnancy issues should be discussed when choosing the most appropriate AED (Tomson and Battino 2005; Tomson et al. 2016) particularly for sodium valproate (Tomson et al. 2015). In resistant cases benzodiazepines are worthwhile. Lamotrigine has been used with variable effect on myoclonic jerks, including aggravation in rare cases (Crespel et al. 2005). The combination of low doses of lamotrigine and of sodium valproate may be efficacious when monotherapy is insufficient. A randomised double-blind control study showed clear efficacy.
of levetiracetam for myoclonic jerks in JME (Vedru et al. 2005) and the use of this agent is now widespread. Topiramate, zonisamide and most probably perampanel are useful alternatives.

A particular profile of pharmacosensitivity of JME, similar to that of other idiopathic generalised epilepsies, has been described by Thomas et al. (2006) who stressed the potential for seizure aggravation with phenytoin, and particularly carbamazepine which could precipitate myoclonic status. Seizure prevention involves the promotion of good sleep hygiene as sleep deprivation is a reliable provoking factor.

Response to treatment is usually excellent, with complete control observed in approximately 80–90% of cases, although remission is rare. Seizure relapse after discontinuation of medication is frequent, even after many years of seizure control, but may not occur for several years (Thomas et al. 2005). Prognosis should be discussed, particularly with adolescents who are seizure-free for years. If a trial of discontinuation is initiated, advice regarding driving must be provided.

Diagnosing JME is usually easy. However, rare progressive myoclonus epilepsies, like Lafora disease and some cases of Unvverricht–Lundborg disease must be ruled out, as their onset may mimic JME (see Progressive Myoclonus Epilepsies section). Subsequent worsening of the myoclonic syndrome, appearance of slow background EEG activity and cognitive deterioration all suggest the possibility of a progressive disorder (Arzimanoglou et al. 2004).

Genetic factors play an important causal role in this syndrome (see Table 16.2). Genetic studies (review in Thomas et al. 2005) report linkage to the short arm of chromosome 6 or long arm of chromosome 15. However, family studies of transmission are often contradictory. A polygenic model is considered most probable (Bate and Gardiner 1999), and might account for the ambiguous and contradictory results of linkage studies that are based on simple, Mendelian models of transmission. This polygenic model assumes a common core of genes that lower the epileptogenesis threshold in the idiopathic generalised epilepsies; the specific expression of JME is thus considered a consequence of dysfunction in one or several other genes (Sander et al. 2000). Additional ion channel genes are likely to be identified in JME, and there is growing evidence that non-ion channel genes are also associated with the disease. Indeed, mutations in the EFHC gene have recently been associated with familial JME (Suzuki et al. 2004), whereas polymorphisms in BRD2 (Pal et al. 2003) and MAE (Greenberg et al. 2005) are associated with complex inheritance in JME.

Eyelid Myoclonia with Absences (EMA)

This disorder is characterised by the frequent occurrence of eyelid jerks with upward eye deviation that is variably associated with a brief loss of awareness (Jeavons 1982; Appleton et al. 1993; Panayiotopoulos 1998). The EEG reveals short duration polyspike–wave complexes (<6 seconds) and photosensitivity. Treatment with sodium valproate or other AEDs indicated in the idiopathic generalised epilepsies, is effective.

PROGRESSIVE MYOCLONUS EPILEPSIES

The progressive myoclonus epilepsies (PMEs) are a group of symptomatic generalised epilepsies caused by rare diseases that are mostly genetic in origin (Shahwan et al. 2005; Minassian et al. 2016). Mitochondrial disorders, especially the syndrome of myoclonic encephalopathy with ragged red fibres (MERRF), however, can produce a similar clinical picture (see Chapter 9).

The history of PMEs spans more than a century (Genton et al. 2016) but their nosological framework originated with the Marseille School in France. The late Jo Roger, wrote that the:

PME syndrome is characterised clinically by the association of the following:

1. A myoclonic syndrome associating generalised myoclonus and arrhythmic asynchronous and asymmetrical, partial or segmental myoclonus;
2. An epilepsy syndrome in which the seizures are of various types, the most frequent being generalised tonic–clonic seizures, myoclonic seizures and tonic seizures;
3. Progressive cognitive deterioration leading to dementia;
4. A neurological syndrome generally associating cerebellar, pyramidal and eventually extrapyramidal signs.

On the EEG, there exists a progressive deterioration of the background rhythm, a progressive alteration in the organisation of the sleep patterns and paroxysmal abnormalities … (Roger 1985).

It was already known that the term PME includes a wide spectrum of different aetiologies that were mostly unknown at that time. However, the concept served as a practical basis for electroclinical diagnoses and better delineation of the syndromes (Marseille Consensus Group 1990). The inclusion of less heterogeneous subgroups and a better understanding of the underlying pathophysiological mechanisms has resulted in ‘the Gene-Empowered era of the PMEs’ (Minassian et al. 2016).

Disorders with myoclonus and myoclonic epilepsy are given in Table 16.13. Myoclonic epilepsies with known metabolic defects are considered in Chapter 9 and Neuronal Ceroid-Lipofuscinoses (NCLs) in Chapter 10. The reader is also referred to reviews by the Marseille Consensus Group (1990), and the recently published state-of-the-art supplement edited by Minassian et al. (2016).

In the present section, we will only discuss two of the PMEs that, particularly at onset in early adolescence, may be misdiagnosed as JME. Both Unverricht–Lundborg and Lafora disease combine generalised tonic–clonic seizures or massive myoclonic jerks, localised myoclonus that may be spontaneous but is often induced by external stimuli such as touch, action or intention, and various degrees of neurological and cognitive deterioration.
Chapter 16 Epilepsy and Other Seizure Disorders

Unverricht–Lundborg Disease (Baltic Myoclonus, Ramsay Hunt Syndrome, EPM1)

Unverricht–Lundborg Disease (ULD) is the best example and the most common of the degenerative myoclonic epilepsies. It is transmitted as an autosomal recessive condition and is due to an unstable dodecamer repeat located in the promoter region of the cystatin B gene, a cysteine protease inhibitor, on chromosome 21. This mutation is associated with a deficiency of cystatin B messenger RNA in some cell types. In some cases, other mutations such as splicing errors or other point mutations resulting in loss of function of cystatin B have been reported (Lehesjoki 2003). The pathology is limited to the cerebellum with loss of Purkinje cells and occasionally of neurons in deep cerebellar nuclei and the inferior olive (Friede 1989; Koskineni et al. 1994).

Onset of the clinical manifestations occurs between the ages 6 and 16 years with tonic–clonic seizures in 50% of cases and myoclonic seizures in the other half (Koskineni et al. 1974a). The myoclonus disappears during sleep or rest and is induced by external stimuli but mainly by maintenance of posture or intended movement. Its intensity increases progressively and it may become totally incapacitating in adulthood. Epileptic seizures are seldom severe and include generalised tonic–clonic seizures, often occurring on awakening, and massive myoclonic jerks very similar to those in juvenile myoclonic epilepsy. Absences or drop attacks occur in a minority of patients.

Intelligence is relatively preserved but there is often slow mild deterioration attributed most often to phenytoin treatment. Kyllerman et al. (1991) reported the occurrence of ‘cascades’ of seizures and myoclonic jerks. Neurological signs including intention tremor appear after a few years; pyramidal tract signs occur in one-third of cases (Berkovic et al. 1993). Cerebellar signs are difficult to assess because of intention myoclonus.

The EEG reveals variable slowing of background activity with superimposed paroxysmal activity (Koskineni et al. 1974b). Background rhythms may remain normal for many years despite the paroxysmal abnormalities, a scenario identical to the primary generalised epilepsies. Runs of spikes appear at the vertex during REM sleep. These differences are considered to be of nosological significance by some investigators who prefer to separate a subgroup of Mediterranean myoclonus from the Baltic form that corresponds to the original description of Unverricht. It is now known that cases of Baltic myoclonus and Mediterranean myoclonus or Ramsay Hunt syndrome (Tassinari et al. 1989) represent the same disease. Both are linked to the same locus on chromosome 21 (Cochius et al. 1993), and the same mutation has been found in both Finnish and Italian cases (Parmeggiani et al. 1997). Giant somaesthetic evoked potentials are recorded in all cases, indicating a cortical-type myoclonus (Shibasaki et al. 1986).

Given the absence of specific clinical or pathological markers, confirmation of ULD is based on genetic analysis. While diagnosis formerly relied on a combination of positive signs in the absence of more specific symptoms and markers of other PMEs, molecular biological techniques are now in widespread clinical use. However, given the cost of genetic diagnosis, we agree with Crespel et al. (2016) that this procedure should follow solid electroclinical evidence rather than screening for all possible genetic aetiologies in poorly assessed participants with epilepsy and myoclonus.

Treatment is oriented to preventing the intention myoclonus. Sodium valproate, primidone, clonazepam (or clobazam) and 5-hydroxytryptophan, sometimes in combination, may be effective (Obeso et al. 1989). Piracetam in very large doses has been shown to be efficacious for myoclonus, and levetiracetam may also be of benefit (Crest et al. 2004). Phenytin

### Table 16.13 Diseases featuring progressive myoclonus epilepsy (PME)

<table>
<thead>
<tr>
<th>Diseases in which PME is pure or in forefront of clinical picture</th>
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<tbody>
<tr>
<td>Lafora disease (PME1, PME2A, PME2B)</td>
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<tr>
<td>Unverricht–Lundborg disease†</td>
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<tr>
<td>Myoclonic epilepsy with ragged-red fibres (MERRF) (Chapter 9)</td>
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<tr>
<td>Juvenile Gaucher disease (Type III) (Chapter 9)</td>
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<tr>
<td>Hereditary dentatorubral–pallidolusian degeneration</td>
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<tr>
<td>PME with lipomas (Ekbom syndrome) (Berkovic et al. 1993)†</td>
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<tr>
<td>PME with deafness (May–White syndrome)†</td>
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<td>PME with renal failure (Badhwar et al. 2004)</td>
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<th>Diseases in which PME is atypical or associated with other manifestations</th>
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<tr>
<td>Neuronal ceroid–lipofuscinosis (several types)</td>
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<tr>
<td>Alpers poliodystrophy and related mitochondrial disorders†</td>
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<tr>
<td>Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)</td>
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<tr>
<td>Huntington chorea (myoclonic form) (Gambardella et al. 2001)</td>
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<tr>
<td>Hallervorden–Spatz disease</td>
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<td>Bioprotein deficiency (Chapter 9)</td>
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<th>Diseases in which PME is overshadowed by other manifestations</th>
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<tr>
<td>Nonketotic hyperglycinæmia</td>
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<td>D-glyceric aciduria Bioprotein deficiency</td>
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<td>Menkes disease</td>
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<td>Krabbe disease</td>
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<td>Tay–Sachs disease</td>
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<tr>
<td>Sandhoff disease</td>
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<tr>
<td>Niemann–Pick disease</td>
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<tr>
<td>Spinal muscular atrophy and progressive myoclonic epilepsy (Striano et al. 2004)</td>
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<tr>
<td>Myoclonic epilepsy and acute intermittent porphyria (Varsik et al. 2005)</td>
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†The same (or a very similar) disorder is referred to as Ramsay Hunt syndrome in some publications (Genton et al. 2005).

‡These syndromes are probably related to mitochondrial disorders.
may aggravate incapacity and is, therefore, contra-indicated. Commonly used combinations include sodium valproate with levetiracetam, topiramate or zonisamide, with the eventual addition of benzodiazepine (Crespel et al. 2016). The use of perampanel is under evaluation. Vagal nerve stimulation has limited benefit. The benefit of deep brain stimulation is unknown.

The prognosis of ULD is poor from a functional standpoint, but with modern treatment the disease is rarely life threatening. The term Ramsay Hunt syndrome should be abandoned as some investigators believe it designates a disorder identical with or similar to ULD. For other authors (Marseille Consensus Group 1990) it applies to a progressive ataxia associated with intention myoclonus, with or without epilepsy but accompanied by cerebellar signs.

A second type of recessive progressive myoclonus epilepsy with similar clinical features but without mutations in the cystatin B gene has been described in an inbred Arab family, mapping to the pericentric region of chromosome 12 (Berkovic et al. 2005).

**Lafora Disease**

Lafora disease (EPM2) (Turnbull et al. 2016) is the best-defined type of progressive myoclonus epilepsy with a detectable storage. Lafora (amyloid) bodies are found within neurons throughout the neuraxis, especially substantia nigra, dentate nucleus, reticular substance and hippocampus. They are also present in muscle, liver, and sweat gland ducts, thus permitting diagnosis by skin biopsy. Biochemically, Lafora bodies consist of a glucose polymer chemically related to glycogen in association with protein. These neurotoxic polyglucosans accumulate in the endoplasmic reticulum where they are normally cleared by the protein laforin, a dual-action phosphatase.

The disease is inherited as an autosomal recessive trait, and two different loci and genes have been found: EPM2A has been mapped to chromosome 6q24 and codes for laforin; EPM2B on chromosome 6p22 codes for a different protein, malin (Chan et al. 2003), with no substantial genotype–phenotype differences between the two. Founder effects and recurrent mutations are common, and mostly isolated to specific ethnic groups and/or geographical locations. The EPM2A and EPM2B mutations were responsible respectively for 70% and 27% of the 54 cases studied by Gomez-Abad et al. (2005), but the proportions vary with the populations studied (Franceschetti et al. 2006).

Clinical onset occurs between ages 6 and 19 years and in 80% of cases is marked by epileptic seizures, mainly myoclonic, clonic or tonic–clonic. Focal seizures with visual symptoms are reported in half the cases. Erratic, fragmentary myoclonic jerks and massive myoclonias are common and exaggerated by movement and intention. Intellectual disability is often rapidly progressive but may be absent for several years. Pyramidal, extrapyramidal and cerebellar signs appear after a variable delay.

The EEG initially reveals polyspike–wave discharges. Background rhythms then become progressively slower. Death occurs, on average, 5–6 years after onset. Axillary skin biopsy is optimal for diagnosis, although pitfalls in interpretation are known to exist (Andrade et al. 2003). Liver and muscle biopsy also reveal the polyglucosan storage.

Ganesh et al. (2002) reported on a different ‘sub-phenotype’ with childhood onset of dyslexia and other specific learning difficulties, followed by epilepsy and neurological deterioration in association with mutations in exon 1 of the EPM2A gene.

Differential diagnosis includes the idiopathic generalised epilepsies, especially the juvenile form, which may be very difficult to separate at onset. EEG slowing may be the first worrisome symptom. Other degenerative and metabolic epilepsies may also cause diagnostic uncertainty. Rarely, a negative skin, muscle or liver biopsy or a negative search for EPM genes has not excluded the diagnosis which is subsequently made only by brain biopsy (Al Otaibi et al. 2003).

There is no specific therapy, only the symptomatic treatment of epilepsy. Social support is vital (Turnbull et al. 2016) and psychological support is available from patient organisations. Counselling is useful during the early stages of the condition. Physical therapy maintains optimal muscular condition and prolongs ambulation.

**Other Myoclonic Syndromes**

These include late cases similar to benign myoclonic epilepsy of infancy but with a late onset up to 5–6 years of age (Guerrini et al. 1994a) and self-induced photomyoclonic seizures.

An autosomal dominant association of cortical tremor, myoclonus and epileptic seizures with different acronyms has been reported in many Japanese and European families. This disorder is currently termed familial adult myoclonic epilepsy. Striano et al. (2005) reviewed familial cases and concluded that they are all the same clinical entity even if genetically heterogeneous: Japanese families are linked to 8q24 and Italian families to 2p11.1–q12. A third locus may also be involved and sporadic cases with similar characteristics have also been reported.

**SYNDROMES OF LATE CHILDHOOD AND ADOLESCENCE WITH FOCAL (PARTIAL) SEIZURES**

Focal (partial) epileptic seizures are defined as seizures with onset in a neuronal population limited to one cerebral hemisphere (Fig. 16.12a–d). Focal seizures in children are not necessarily indicative of a localised brain lesion as idiopathic focal epilepsies are frequent. However, the symptomatology of non-idiopathic (structural/lesional) forms may be similar, but a careful analysis of clinical and EEG features will enable correct diagnosis (Kahane et al. 2005).
Continued

Figure 16.12  Focal temporal lobe seizure.  
Continued
Focal seizures of lesonal origin are caused mainly by malformational lesions (including developmental tumours) and destructive lesions of pre-, peri- or postnatal origin. The extent of the causal lesion largely determines the outcome. Large lesions of prenatal origin may involve several lobes and raise formidable problems of treatment. However, even relatively small lesions may have a noxious effect on overall brain function and cause behavioural and cognitive deterioration through poorly understood mechanisms involving aberrant neural circuitry. Early resection of lesions and seizure-freedom will prevent a progressive course.

Two main categories of focal seizures were initially recognised by the ILAE (Commission on Classification and Terminology 1989) depending on the presence or absence of impairment of consciousness. Consciousness is defined operationally as awareness and responsiveness (Commission on Classification and Terminology 1981). Seizures with impairment of awareness and/or responsiveness were termed ‘complex partial seizures’; those without impaired consciousness were termed ‘simple partial seizures’. Although the concept is debatable (Gloor 1986), this scheme has been widely used even in recent publications. The ILAE classification stated that both forms can evolve into generalised seizures, and that simple partial seizures can evolve into the complex form.

Currently, the trend is to use more descriptive terms without necessarily having pathophysiological value (Lüders et al. 1993, 1999; Engel 2001; Arzimanoglou et al. 2004), because loss of consciousness is related to more widespread discharging rather than to a different origin. If propagation is restricted, the clinical expression is a simple partial seizure; if the discharge propagates from the seizure-onset zone the ‘simple’ partial seizure constitutes the aura of the ‘complex partial’ attack.

More recent reports from ILAE Task Forces (Scheffer et al. 2016; Fisher et al. 2017) underscored the need for a pragmatic approach when describing and classifying focal seizures. The use of descriptors (motor versus non-motor; aware/impaired awareness/unknown awareness; motor tonic/hypermotor, etc.) should be privileged and applied individually or in combination with other features depending on the purpose.

Recognising the focal origin of a seizure by obtaining a detailed description of the ictal clinical phenomena is of paramount importance as it will orientate investigation priorities and treatment choices. The next important step is to differentiate, on the basis of clinical examination and EEG data, ‘functional’ (idiopathic) from lesonal (non-idiopathic) epilepsies and correlated with neuroimaging investigations. The latter should be correlated based on a localising hypothesis from the clinical semiology. A more detailed analysis of the cortical anatomy of epileptogenesis is required for purposes of localisation and surgery.

Various seizure types are listed in Tables 16.6 and 16.7. Their clinical expression reflects the origin and propagation of the epileptic discharge.

Focal epilepsies of childhood can be conveniently divided into two groups: idiopathic focal epilepsies, in most cases genetic (for a review see Pal et al. 2016) and non-idiopathic (structural and/or genetic) types.

**Self-Limited (Idiopathic, Genetic)**

**Focal Rolandic Epilepsy**

Rolandic epilepsy (also described as benign partial epilepsy of childhood with centrotemporal spikes [BECTS]) is
the most common syndrome of idiopathic focal epilepsy in childhood and one of the best-defined, self-limited, epilepsy syndromes. Fifteen to 25% of school-age children with epilepsy are affected (Heijbel et al. 1975; Dalla Bernardina et al. 2005). The syndrome is believed to be genetic in origin but whether a dominant or multifactorial transmission is responsible is unknown, although the latter seems more likely (see Table 16.2). Recent twin studies (Vladlamundi et al. 2006) have challenged the genetic hypothesis and emphasise the importance of acquired factors. The issue is complicated because fewer than 10% of children with rolandic spikes have seizures, and the EEG abnormalities are themselves a heritable trait. Foci of characteristic rolandic sharp waves are frequently encountered in children without epilepsy and their diagnostic value, when isolated, is, therefore, limited.

Age at onset is almost always between 2 and 13 years, with rare cases recorded as early as 1 year. The typical seizures are ‘simple partial seizures’, preferably termed focal motor seizures without impaired consciousness. They are mainly motor in expression, although buccal or labial paraesthesiae are common, and preferentially involve the facial and oropharyngeal musculature, with resulting salivation and/or speech arrest. Individual seizures are brief (30–60 seconds). Sixty to 80% of seizures occur during asleep or upon awakening. Secondary generalisation occurs in 20% of patients, mainly nocturnally, while pure motor seizures tend to occur on falling asleep or awakening. Postictal transient paresis (Todd paralysis) can be observed. Most children have rare seizures, and the response to antiepileptic drugs is favourable, indicating a low epileptogenicity of the focus, which remains clinically silent in over 90% of cases (Arzimanoglou et al. 2004; Dalla Bernardina et al. 2005).

Patients with rolandic epilepsy have a normal neurological examination, and most achieve normal neurodevelopmental progress. However, language difficulties of mild to moderate severity are being increasingly recognised (Staden et al. 1998; Deonna 2000; Saint-Martin et al. 2001a; Pinton et al. 2006). In a case-control study, Weglage et al. (1997) found frequent visuomotor and spatial difficulties in children with centrotemporal spikes.

The EEG abnormality in rolandic epilepsy consists of a focal negative diphasic slow spike, of medium to high voltage, followed by a slow wave located in the centrotemporal areas with a field that may include adjacent regions superimposed on a normal background (Fig. 16.13). A more posterior predominance is often observed in younger individuals. Discharges may occur in isolation or in brief runs (Fig. 16.14). Temporary disappearance and migration of paroxysms between hemispheres is frequently observed. The electrical field is represented as a horizontal dipole (frontal positivity and maximum negativity posteriorly in the rolandic region). Activation in drowsiness and sleep is a hallmark. Localisation over the upper rolandic area is also possible but the middle area is not involved (Legarda et al. 1994). However, unusual localisations are not infrequent (Wirrell et al. 1995) and the characteristic stereotyped spike morphology is more important for diagnosis than precise topography. Yet, paroxysms morphologically similar to benign focal epilepsy may also exist in epilepsies due to brain injury (Gobbi et al. 1989; Santanelli et al. 1989; Ambrosetto 1992). As reported by several authors...
Part VII Paroxysmal Disorders

(for reviews see Dalla Bernardina et al. 2005; Pal et al. 2016), the most striking finding of centrotemporal spikes is the significant increase in frequency during drowsiness and all stages of sleep. They appear only during sleep in approximately 30% of children.

The outcome of rolandic epilepsy in terms of seizures is extremely favourable. Up to 25% of children have only one seizure and most have only a few episodes the occurrence of more frequent seizures does not alter outcome. Recurrence after age 16 years is exceptional (Loiseau et al. 1988). Occasional generalised tonic–clonic seizures have been observed in a few adult patients after the resolution of rolandic epilepsy, and a few cases of status epilepticus have also been reported. Prognosis for school and social functioning is favourable (Loiseau et al. 1983).

Following the description by Aicardi and Chevrie (1982), several investigators have reported on atypical aspects of benign partial epilepsy (Fejerman et al. 2000; Saint-Martin et al. 2001a). A few children with rolandic foci and occasional nocturnal seizures experience atonic and/or myoclonic seizures, often grouped in clusters and repeated multiple times daily. This group was termed atypical benign partial epilepsy or Aicardi-Chevrie syndrome (Aicardi 2000; Fejerman et al. 2000) or pseudo-Lennox syndrome (Hahn et al. 2001) based on the atonic seizures and severe EEG anomalies. Atonic seizures are particularly prominent and may occur several dozen times daily, often with falls. The clusters may last 2–3 weeks separated by several months. The sleep EEG is similar to cases of continuous spike–waves during slow sleep (Aicardi and Chevrie 1982; Aicardi and Levy Gomes 1992), and the awaking EEG reveals multiple bilateral spike–wave discharges. Affected patients may be erroneously diagnosed with LGS because of their falls and the severe nocturnal paroxysmal activity. Although the course of this syndrome may be favourable with spontaneous remission before the age of 10 years and after two or more clusters, cases with a more severe outcome are known (Hahn et al. 2001). Cognitive and behavioural abnormalities can persist but have not been studied in detail. A precise nosology of this syndrome is not yet established (Deonna et al. 1986) but clearly fits within the spectrum of epilepsies with an EEG pattern of continuous spike–waves during sleep (CSWS). The atonic episodes may represent partial or secondarily generalised negative myoclonus. Such episodes have been reported in patients with benign partial epilepsy treated with carbamazepine (Caraballo et al. 1989). However, many patients with this syndrome have not received this drug (Aicardi and Levy Gomes 1992).

Episodes of opercular status epilepticus involving the face, tongue and pharyngo-laryngeal structures have been observed (Saint-Martin et al. 1999). The EEG reveals rhythmic spike–wave discharges with the spikes synchronising with facial jerking. Pseudobulbar symptoms such as drooling and dysarthria may be observed (Roulet et al. 1989; Bouloche et al. 1990; Deonna et al. 1993; Fejerman et al. 2000) and true aphasia is noted occasionally (Roulet et al. 1989). Some patients required corticosteroids for control (Fejerman and Di Blasi 1987).
Scheffer et al. (1995b) observed severe and permanent speech dyspraxia and difficulties of oro-buccal movements in several members of a family with an autosomal dominant inheritance and possible anticipation. Guerrini et al. (1999) reported the occurrence of paroxysmal activity in the form of writer’s cramp and ataxia as an autosomal dominant syndrome, but this condition is different from the usual benign presentation. Recently, Roll et al. (2006) have identified the Xq22 gene SRPX2 in patients with rolandic seizures associated with oral and speech dyspraxia and intellectual disability.

The common or typical form of rolandic epilepsy is likely to have a complex genetic inheritance. The genetic basis is unknown despite the recent identification of a low frequency of mutations (5% of cases) in the postsynaptic glutamate receptor subunit GRIN2A (Carvill et al. 2013; Lemke et al. 2013) and DEPDC5, a cell growth regulator in the mTOR pathway (Lal et al. 2014). Other potential new candidate genes, RBFOX1 and RBFOX3 (Lal et al. 2013) have also been reported.

**Self-Limited (Idiopathic, Genetic) Occipital Epilepsies**

The occipital epilepsies of childhood form a heterogeneous group (Covanis et al. 2005; Pal et al. 2016). The most common type is an idiopathic and benign epilepsy initially described by Panayiotopoulos and now termed Panayiotopoulos-type occipital epilepsy or Panayiotopoulos syndrome.

**Panayiotopoulos-type occipital epilepsy**

Onset occurs in developmentally typical children between 1 and 10 years, with a maximum incidence around 3–4 years. Seizures are generally infrequent and occur mostly during sleep. They are marked mainly by eye deviation with disturbances of awareness that are difficult to assess in sleep. Autonomic symptoms are prominent, especially vomiting. The seizures most often last a few minutes but are often prolonged with up to 44% of cases (Ferrie et al. 1997) lasting minutes to hours with vomiting, unconsciousness and eye deviation. These seizures are easily mistaken for coma of toxic or metabolic origin (Panayiotopoulos 1989, 2000; Kivity and Lerman 1992) or emergency abdominal problems. Long-lasting seizures may culminate in prolonged unilateral convulsions. Atypical cases may also manifest as syncope that is difficult to differentiate from cardiac or vasovagal episodes. Visual symptoms are rare (see below for differential diagnosis with the Gastaut-type occipital epilepsy) but postictal headache is frequent.

The interictal EEG typically reveals paroxysmal activity localised to or predominating in the occipital area uni- or bilaterally, but is occasionally normal. Intermittent discharges can be decreased or arrested by visual fixation. Such cases may constitute the most common benign epilepsy syndrome under the age of 5 years and are probably related to rolandic epilepsy. The extent of the syndrome is not fully defined: some atypical manifestations such as syncope and prolonged coma may be misleading; from the EEG point of view, the localisation and appearance of the paroxysmal activity is often variable as predominant extra-occipital paroxysms are noted in 10% of cases (Panayiotopoulos 2002). This group is often benign, although occasional atypical cases have been reported (Ferrie et al. 2002; Kikumoto et al. 2006).

**Gastaut-type occipital epilepsy**

This syndrome, is characterised by focal seizures with predominantly visual symptoms, associated with the presence of continuous or rhythmical, spike–wave activity over one or both occipital areas that is arrested or considerably diminished by eye opening. Onset occurs between 3 and 9 years (Gobbi and Guerrini 1998). Ictal visual manifestations may consist of negative (transient loss of vision) or positive symptoms such as simple visual hallucinations of colours and/or geometric shapes (Aso et al. 1987; Thomas et al. 2003). Non-visual seizures may also be the presenting or sole symptom (Panayiotopoulos et al. 1989). Postictal headache, often migrainous, occurs in one-third of cases.

**Idiopathic Partial Photosensitive Epilepsy**

This is a rare form of idiopathic occipital epilepsy (Guerrini et al. 1994b, 1995). Seizures are characterised by visual phenomena that are often long-lasting with a slow progression of the visual abnormalities. The syndrome is usually responsive to treatment and has a favourable outcome.

The overall outcome of the idiopathic occipital epilepsy syndromes is generally favourable but ‘benign’ cases may be difficult to distinguish from symptomatic cases in brain-damaged children (Newton and Aicardi 1983; Dalla Bernardina et al. 1993). For this reason we recommend the realisation of an MRI investigation for all children with occipital seizures.

**Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)**

More recently, several new syndromes predominantly characterised by focal seizures unassociated with brain lesions have been reported. Some are genetically transmitted (Picard et al. 2000; Pal et al. 2016), mostly in a dominant manner, and a several genes have been identified. Evidence for genetic transmission is based on pedigree studies, and a genetic origin has only rarely been convincingly demonstrated.

The most important of these newly described syndromes are autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and familial temporal lobe epilepsy (FTLE), the latter being reported only in adults. Familial epilepsy with multiple foci (Scheffer et al. 1998), FTLE with and without auditory symptoms and autosomal dominant rolandic epilepsy with speech dyspraxia have been observed in rare families (Andermann and Kobayashi 2005).
The diagnosis of ADNFLE may be suspected on clinical grounds. This disorder is characterised by brief hypermotor nocturnal seizures with hyperkinetic or tonic manifestations. Patients often experience an aura (fear, forced thinking) and may remain conscious throughout the events. Seizures are brief and stereotyped and mainly tonic or dystonic. They often recur in clusters of several episodes in one night, especially in drowsiness or shortly before awakening.

The epilepsy can begin at any age but usually presents in childhood and is usually life-long with considerable variations in severity. Interictal EEG studies are often non-diagnostic as the seizure-onset zone is typically a deep hemispheric source. Focal theta or delta rhythms or sharp waves may be recorded in the frontal area. Frustratingly, the ictal EEG is often unhelpful due to movement and muscle artefact. Most cases respond to carbamazepine, but up to 30% of cases may be difficult to control. Neuroimaging is normal.

Scheffer et al. (1995a) originally described 47 affected persons in five families and other cases have now been reported (see Picard et al. 2000). Molecular genetic testing reveals pathogenic variants in CHRNA4, CHRNB2, CHRNA2, KCNT1, DEPDC5 or CRH in approximately 20% of individuals with a positive family history but in fewer than 5% of individuals with a negative family history (Kurahashi and Hirose 2015). The disorder has an autosomal dominant inheritance with a high penetrance (see also Table 16.2).

Only the autosomal dominant form of nocturnal frontal lobe epilepsy is included within the guidelines proposed by the ILAE Commission on Classification and Terminology. To improve the definition of the disorder and establish diagnostic criteria with levels of certainty, a consensus conference using formal recommended methodology was held in Bologna in 2014 (Tinuper et al. 2016). It was recommended that the name be changed to sleep-related hypermotor epilepsy (SHE), reflecting evidence that the seizures occur in sleep rather than wakefulness, arise from pre-frontal sites, and have stereotyped motor characteristics. The aetiology may be genetic or due to structural pathology, but most cases remain unknown. Diagnostic criteria were developed with three levels of certainty: witnessed (possible) SHE, video-documented (clinical) SHE and video-EEG-documented (confirmed) SHE.

Diagnosis may be difficult to establish as the ictal manifestations resemble some types of parasomnias and pseudoseizures. Dystonic seizures are probably identical to those described as nocturnal dystonia by Lugaresi et al. (1986). The nosological situation of ADNFLE and related cases remains unclear. A genetic basis has not been established in many cases, and sporadic cases and phenocopies may exist. Small areas of dysplasia in MRI-negative cases may mimic symptoms, and their presence is an important consideration. Localising the seizure onset zone may require ancillary studies such as PET or SPECT. Although a frontal lobe location is likely in most cases, onset outside the frontal lobe may have similar clinical characteristics (Arzimanoglou et al. 2004). Ryvlin et al. (2006) reported cases with a similar semiology that proved to be of insular origin.

Familial Temporal Lobe Epilepsy (FTLE)

Berkovic et al. (1996) described idiopathic cases in adults with a dominant transmission, a favourable course and symptoms suggesting mesial temporal epilepsy. To date, no case has been described in children. This ‘syndrome’ is defined by genetic data, as the clinical and EEG features do not differ significantly from those of more common temporal lobe epilepsies. The recognition that not all cases of temporal lobe epilepsy are due to underlying injury or are intractable is clearly significant for evaluation and prognosis.

To assess the clinical impact of DEPDC5 (DEP domain-containing protein 5) mutations in familial temporal lobe epilepsy, an Italian group (Striano et al. 2015) screened families with either autosomal dominant lateral temporal epilepsy (ADLTE) or familial mesial temporal lobe epilepsy (FMTLE). The probands of 28 families were classified as ADLTE and 17 families with FMTLE were screened for DEPDC5 mutations by whole exome or targeted massive parallel sequencing. They identified a DEPDC5 nonsense mutation (c.918C>G; p.Tyr306*) in only one family with two affected members, clinically classified as FMTLE. The proband had temporal lobe seizures with prominent psychic symptoms (déjà vu, dissociated and forced thinking); her mother had temporal lobe seizures, mainly consisting of visceral epigastric auras and anxiety. In total, they found a single DEPDC5 mutation in one of (2.2%) 45 families with genetic temporal lobe epilepsy, a proportion much lower than in other inherited focal epilepsies.

A second type of familial temporal lobe epilepsy with dominant inheritance is characterised by the presence of auditory ictal symptoms (Ottman et al. 1995; Cendes et al. 2005). This syndrome presents as a relatively mild epilepsy characterised by focal seizures with elementary auditory hallucinations, often generalised tonic–clonic seizures and dominant inheritance. Other symptoms, especially ictal dysphasia, may occur (Bisulli et al. 2004; Ottman et al. 2004). Response to medication is usually favourable. A gene (LTI1/petemipin), mapped to chromosome 10q is responsible for some cases but other cases are not linked to this locus and sporadic cases are described (Bisulli et al. 2004).

Non-Idiopathic (Structural and/or Genetic) Focal Epilepsy Syndromes per Lobe

‘Non-idiopathic focal epilepsies’ refer to all focal epilepsies known or suspected to result from a brain lesion or abnormality. The terms ‘symptomatic’, ‘probably symptomatic’ or ‘cryptogenic’ are also used in the literature. As opposed to the much better defined category of idiopathic focal epilepsies, non-idiopathic focal epilepsies are a heterogeneous group of conditions with differing aetiology, pathology and clinical presentations (Arzimanoglou et al. 2004; Kahane et al. 2005), including genetic factors responsible for the brain lesions. The clinical expression of lesional epilepsy may not differ from idiopathic seizure expression.
Only a few reasonably well-defined syndromes are defined among the epilepsies of lesional origin (e.g., mesiotemporal epilepsy). The so-called topographic syndromes (frontal, temporal, parietal and occipital epilepsies) may designate large anatomical regions of seizure onset. Even within a same lobe, clinical semiology may differ and interictal or ictal EEG abnormalities are not a constant feature. Furthermore, prominent clinical symptoms often result from seizure propagation and do not necessarily indicate the seizure-onset zone. Consequently, the definition (and description) of the various focal non-idiopathic epilepsies is based on detailed description of the seizures and interictal EEG abnormalities. Thus, their cause and prognosis are often determined through an individual combination of signs and symptoms from multiple investigations, particularly neuroimaging, interictal and ictal EEG.

Accurate description of the semiology of focal seizures is especially important for topographic diagnosis and for a better orientation of the neuroimaging investigations. Clinical manifestations and ictal and interictal EEG features help localise seizure origin to a specific cortical area. However, epileptogenesis is a dynamic process and often propagates to neighbouring and distant areas by both normal and abnormal pathways.

Similarly, the relationship between the location of a lesion and that of the resulting epileptic discharge is complex, and there is no absolute concordance. With these reservations in mind, some elements of localisation can be tentatively described in topographic syndromes. What follows is a very brief description of their main characteristics.

Children with drug-resistant focal seizures of lesional origin typically harbour dysplastic lesions (Blümcke et al. 2011), developmental tumours or destructive lesions of pre-, peri- or postnatal origin. The extent of the causal lesion largely determines the diagnostic approach. Large lesions of prenatal origin may involve several lobes and raise formidable problems of treatment. However, even relatively small lesions may have a noxious effect on overall brain function and lead to behavioural and cognitive deterioration. Early resection of lesions may prevent the appearance of epileptic encephalopathy and improve long-term prognosis (Arzimanoglou et al. 2016c). Children with focal cortical dysplasias, particularly of the FCD ILAE Type II (Blümcke et al. 2011) are excellent candidates for excisional epilepsy surgery, particularly if the lesion spares eloquent cortex.

**Frontal lobe seizures**

Seizures of extratemporal origin in children are more frequent than those of temporal origin. Seizures of frontal lobe origin are the most common in large surgical series. The diagnosis of frontal lobe epilepsy may be challenging as their semiology may mimic nonepileptic paroxysmal events (sleep disorders or psychogenic seizures). Their presentation typically includes contralateral clonic movements, uni- or bilateral tonic motor activity and complex automatisms (Bancaud and Talairach 1992; Chauvel et al. 1992; Kellinghaus and Lüders 2004). Frontal lobe seizures are often nocturnal, maximal at onset, repetitive, usually of brief duration and having minimal or lacking post-ictal manifestation. Complex motor automatisms (hypermotor seizures) including thrashing of the extremities, body rocking and bicycling leg movements typically begin in the anterior to motor cortex (Licchetta et al. 2017). Other, less specific manifestations are also frequent: arousal from sleep; staring spells during wakefulness and sleepwalking. The yield of surface EEG may be limited due to the difficulty in detecting mesial or basal foci, and a diagnosis of nonepileptic events is common. Mesial frontal foci may be miss-lateralised (‘paradoxical lateralisation’). Anatomical and functional neuroimaging techniques, particularly MRI with epilepsy-specific sequences has helped delineate the epileptogenic source and specific aetiology in an increasing number of patients. Small tumours or dysplasias are the most frequently encountered aetiologies.

Salanova et al. (1995b) studied 150 seizures in 24 adolescent and adult patients. Symptoms and signs could be clustered into three groups:

1. **Supplementary motor area group** (n=9). Seizure discharges involving the supplementary motor area and adjacent frontal lobe, are associated with preserved consciousness. A sensory aura could be reported but the manifestations were predominantly motor with tonic contraction of one or both arms, sometimes with a classic f ‘fencing’ posture, head version, bilateral tonic extension of the trunk or neck and vocalisation. As consciousness is preserved, these motor manifestations may be mistaken for generalised or pseudoseizures (Bass et al. 1995; Laskowitz et al. 1995), however, they are usually symptomatic of a mesial frontal or precentral frontal lesion involving the supplementary motor area.

2. **Focal motor group** (n=7). Seizures in the vicinity of the frontal eye fields produce unilateral, face and/or arm clonic seizures, speech arrest, blinking and head version. Preservation of consciousness was an almost constant feature.

3. **Complex partial seizures group** (focal seizures with impaired awareness according to the most recent terminology) (n=8). In five patients, seizure onset was characterised by ‘staring’ or ‘looking ahead’. Partial or complete unresponsiveness was present in all cases. Although unilateral or bilateral arm tonic posture was similar to that of patients with supplementary motor area seizures, this symptom was never observed at seizure onset. Oroalimentary automatisms occurred rarely toward the end of the seizure.

In much younger children, motor features are common but their characteristics may differ (Fogarasi et al. 2016; Tinuper et al. 2016). Fogarasi et al. (2001) analysed 111 videotaped seizures from 14 patients aged 3–81 months (mean, 30 months) and with frontal lobe epilepsy (FLE) related to focal cortical dysplasia. Ictal events were categorised into behavioural, consciousness, autonomic and sensory features and motor patterns including tonic, clonic, spasm and myoclonic components. Patients had a high seizure frequency, ranging up to 40 seizures per day, often in clusters. Mean
seizure duration was short (29 seconds) and started in sleep in nearly half the patients. Motor manifestations were most common consisting mostly of tonic–clonic seizures and epileptic spasms. Behavioural change was frequent but hypermotor seizures were absent. Motor features were contralateral to the epileptic focus in five patients, including two with asymmetrical epileptic spasms. Secondly generalised tonic–clonic seizures were not observed, but had been described in two patients. Complex motor automatisms were absent, whereas oral automatisms appeared in three young children.

The same team (Fogarasi et al. 2005) analysed 177 seizures in 35 children (aged 11 months to 12 years) with extratemporal epilepsy (FLE compared to posterior cortex epilepsy) selected by postoperative seizure-free outcome. Twenty patients had FLE, and 15 had posterior cortex epilepsy (PCE). Patients from both groups had daily seizures without significant differences in frequency but evidencing nocturnal dominance in children with FLE ($P<0.05$). Visual aura, nystagmus, and versive seizure activity were observed exclusively in the PCE group, whereas somatosensory aura and hypermotor seizures appeared only in FLE. Tonic seizures were significantly more frequent in FLE ($P<0.01$). Myoclonic seizures, epileptic spasms, psychomotor seizures, atonic seizures, oral and manual automatisms, as well as vocalisation and eye deviation appeared in both groups without significant differences in frequency. The study showed that, especially in infants and preschool children, the characteristic features of adult extratemporal epilepsy were frequently absent.

Children with FLE are particularly at risk of misdiagnosis (Fusco et al. 1990; Stores et al. 1991) because of their unusual clinical features and frequent lack of EEG abnormalities. Automatisms do not involve oromotor movements but are gestural, complex and often violent with rocking, kicking and dystonic activity. The bizarre appearance of these seizures often suggests pseudoseizures, the more so as screaming, shouting and the utterance of abusive language are common.

The clinical and EEG features of FLE were compared to mesial temporal lobe epilepsy (MTLE) in 56 children (FTLE=39; MTLE=17) undergoing video-EEG monitoring for presurgical evaluation (Lawson et al. 2002). Frontal lobe seizures were significantly briefer, had different motor characteristics, were more frequent and occurred predominantly during sleep. The rates of bilateral epileptiform interictal and ictal EEG abnormalities were significantly higher in FLE, and patients were more likely to have a normal MRI.

**Seizures from the Central Region**

Seizures of central hemispheric region including primary sensorimotor cortex exhibit a jacksonian march or narrowly localised clonic or tonic motor phenomena, suggesting primary involvement of the rolandic strip. Tingling, a feeling of electricity and loss of muscle tone are common. Reflex activation of simple motor seizures occurs with sudden contact or the contraction of specific muscles. Facial bucco-lingual, tonic–clonic contractures with aphemia, swallowing, salivation and masticatory movements that are often accompanied by sensory symptoms, including tongue sensations of crawling, stiffness, coldness, gustatory hallucinations, and/or laryngeal symptoms suggest involvement of lower periorbital cortex in the upper bank of the sylvian fissure (Lombroso 1967; Loiseau and Beaussart 1973; Wieser and Williamson 1993). More extensive insular involvement is accompanied by vegetative symptoms, which may be digestive, urogenital, cardiovascular or respiratory. These manifestations are easily misinterpreted as being of temporal lobe origin.

**Insular Lobe Seizures**

Ictal semiology of insular lobe seizures is highly variable. Several clinical signs (emotional sensations; autonomic symptoms such as vomiting, cardiac arrhythmias; automotor or hypermotor manifestations; subjective signs of variable expression, etc.) have been reported (for a review see Dimova 2016). At least three patterns can be distinguished: temporal lobe pattern, in which somatosensory or motor ictal symptoms usually precede the typical mesiotemporal semiology (see below); temporo-perisylvian pattern characterised by laryngeal discomfort, dyspnoea, unpleasant paraesthesias affecting the perioral region or larger somatic territories; frontal lobe seizures pattern with predominantly hypermotor manifestations often preceded by somatosensory symptoms. Overall the semiology in children does not substantially differ from descriptions in adults, although precise descriptions are difficult to obtain from very young children. Ictal scalp EEG abnormalities are often widespread involving multiple lobes which suggests a deep seizure focus.

**Temporal Lobe Seizures**

Seizures of temporal lobe origin (Fig. 16.12a–d) are thought to account for most cases with altered consciousness. However, altered consciousness may be even more common with extratemporal seizures, especially in children (Fusco et al. 1990; Chauvel et al. 1992; Williamson et al. 1993a, b). Seizures with and without alteration of consciousness often coexist in the same patient. Seizures are usually prolonged, lasting 1–2 minutes. Autonomic manifestations, psychic and sensory symptoms represent the whole or only the onset (aura) of a more complex episode evolving with altered consciousness (Bancaud 1987).

Focal seizures of temporal lobe origin in children are generally similar to those in adults (Kotagal et al. 1987; Devinsky et al. 1988) but tend to have an atypical and minimal expression in younger children and only progress to a more characteristic picture with increasing age (Brodkhaus and Elger 1995; Fogarasi et al. 2002; Villanueva and Serratosa 2005). Analysis of video recordings of 29 children aged 18 months to 16 years with temporal lobe epilepsy (TLE) (Brodkhaus and Elger 1995) showed that clinical features of temporal lobe seizures can be misleading in younger children, including symmetrical motor phenomena, postures similar...
to frontal lobe seizures in adults, and head noddng similar to infantile spams. Fogarasi et al. (2002) reached a similar conclusion by performing a video analysis of 83 seizures from 15 children (aged 11–70 months). Parallel with age, the frequency of motor components decreased, and in five of 11 children older than 3 years, motor features were totally absent.

In infants and children under 2 years of age, tonic posturing and head rotation are often the initial and dominant manifestations. The duration of seizures is usually longer than for absences (60–120 seconds) and seizures are followed by a period of confusion or of intense tiredness. Onset is often with behavioural arrest and staring. Oroalimentary automatisms tend to predominate in young children (Duchowny 1987) and include licking, lip-smacking, chewing or swallowing movements, while in older children, gestural automatisms such as fingering or fumbling with clothes are also frequent (Holmes 1986; Wyllie et al. 1993; Fogarasi et al. 2002). In young children, the most common aura is an epigastric sensation often associated with fear. In older children, temporal lobe seizures may be preceded by auras with affective or other psychic phenomena such as hallucinations or illusions affecting various sensory modalities (Arzimanoglou et al. 2004; Fogarasi 2016).

TLE can be schematically divided into those of mesiotemporal or lateral neocortical origin. Mesial temporal lobe syndrome is defined not only on topographic criteria and MRI evidence of hippocampal involvement (Fig. 16.15) but also on clinical, EEG and evolutive features (Cendes et al. 2005). The syndrome frequently occurs in patients with a history of complex febrile convulsions in infancy, with long-lasting unilateral seizures in at least 40% of cases. The initial ictus is followed by a second phase of variable duration. Focal seizures mark the third phase of chronic epilepsy, which often appears during the second half of the first decade; however, earlier onset is not unusual with focal epilepsy starting within a few years after febrile seizure onset (Abou-Khalil et al. 1993; Williamson et al. 1993a; Harvey et al. 1995). This ‘roller-coaster course’ (Berg et al. 2006) of TLE probably explains the very long delays in recognising its intractable character and referral for surgical treatment (Arzimanoglou et al. 2005).

Seizures are marked by behavioural arrest and staring followed by automatisms involving especially the oroalimentary muscles (lip-smacking, licking, swallowing). A significant proportion of these automatisms are conscious (Munari et al. 1994; Ebner et al. 1995). Dystonic posturing of the contralateral arm is often observed (Kotagal et al. 1989), while simple automatisms may involve the ipsilateral arm.

The EEG usually demonstrates an interictal anterior temporal spike focus or paroxysmal theta activity (Gastaut et al. 1985), while the ictal EEG reveals focal discharging that may be diffuse and involve the contralateral temporal lobe. MRI reveals loss of hippocampal architecture and increased T2 signal (Jackson et al. 1990; Cross et al. 1993; Cendes et al. 2005). Hippocampal sclerosis has recently been shown to be a progressive disorder (Fuerst et al. 2003). Progressive mesial temporal volume loss in relation to the duration of epilepsy is probably not limited to the hippocampus but also affects entorhinal cortex and amygdala (Bernasconi et al. 2005).

Fluorodeoxyglucose PET scanning reveals localised hypometabolism while SPECT shows reduced blood flow to the mesial temporal lobe interictically and ictal hyperperfusion (Harvey et al. 1993a, 1995). Both interictal FDG-PET and ictal SPECT appear comparable in utility (Desai et al. 2012). PET is quantifiable and has higher resolution than SPECT, but SPECT ligands have a longer half-life and are easier to use (Gaillard et al. 2009, 2011, 2016). Both PET and SPECT use ligands that are designed to target different physiological processes, but in practice only markers of blood flow have been used in SPECT.

In a prospective randomised study (Wiebe et al. 2001), 80 adult patients with TLE were randomly assigned to surgery (40 patients) or medical treatment for 1 year (40 patients). Twenty-three patients were seizure-free in the surgical group compared to three in the medical group ($P<0.001$). This difference emphasises that surgery is superior to prolonged medical therapy in this patient cohort. Patients in the surgical group had fewer seizures impairing awareness and improved quality of life ($P<0.001$ for both comparisons). Four patients had adverse effects of surgery, and one patient in the medical group died.

Most studies on epilepsy surgery of intractable TLE concern adult patients with a long history of epilepsy, and randomised trials are rare (Engel et al. 2003; Schmidt et al. 2004). Surgical outcome is often favourable (Abou-Khalil et al. 1993). More than two-thirds of patients with drug-resistant
TLE are free of disabling seizures with continued medical treatment after temporal resection. Of those, almost one-third will achieve complete discontinuation of AEDs (Schmidt and Loscher 2003). Extrapolation of these data to children is difficult. Prospective studies are necessary to characterise benign mesial TLE with hippocampal sclerosis, define its incidence and prevalence relevant to the severe form, and determine whether the benign and severe forms represent two different pathophysiological conditions, or fall on a spectrum (Wieser 2004). This differentiation is of extreme importance particularly when discussing evolution, not only in terms of seizures but also in terms of socio-cognitive development (Arzimanoglou et al. 2005). For patients who are compromised by such seizures, referral to an epilepsy surgery centre should be strongly considered early in the course of the disorder since, based on retrospective cohort data in children, failure of a first AED trial accurately predicts refractory TLE at 2 years after onset (Dlugos et al. 2001). The long-term neuropsychological impact of surgery in children with hippocampal sclerosis are only beginning to be understood (Krsek et al. 2016). This is another reason why referral to specialised epilepsy centres, having the capacity to prospectively follow these children and constitute comparable cohorts, is of crucial importance.

Seizures associated with small mesial temporal developmental tumours are very similar in clinical expression (Wyllie et al. 1993; Raymond et al. 1994; Arzimanoglou et al. 2004). Such patients have no antecedent history. Wyllie et al. (1993) emphasised that, contrary to mesial temporal sclerosis in which the ictal and interictal EEG anomalies are usually localised to the anterior temporal area, the EEG is often diffusely abnormal in small tumours diagnosed on MRI. Patients with focal cortical dysplasia represent a heterogeneous group (Blümcke et al. 2011; Desikan and Barkovich 2016). Different age at epilepsy onset and transient responsiveness to AEDs may reflect different dynamics in epileptogenicity of the underlying FCD (Fig. 16.16a–b). Dual pathology is common in children (Mohamed et al. 2001) and may be associated with different pathological mechanisms in patients with and without febrile seizures (Fauser et al. 2006). Recent studies emphasise the role of neuronal glial tumours especially gangliogliomas and developmental neuroepithelial tumours as a cause of chronic epilepsy with long-standing monosymptomatic focal seizures.

To distinguish benign tumours causing drug-resistant epilepsy from other brain tumours, with seizures as an epi-phenomenon, the term LEAT (long-term epilepsy-associated tumours) has been coined by Luyken et al. (2003). In LEATs, seizures are the presenting symptom, usually early in life, tumoural growth, if any, is rather slow and localisation preferentially occurs within the temporal neocortex (Holthausen et al. 2016). Taylor-type and other types of cortical dysplasia are also frequent (Blümcke et al. 2011). These lesions are all highly epileptogenic (Fig. 16.17), and the related epilepsy is resistant to drugs in most cases. This is a rapidly expanding field of knowledge, as improved imaging and genetic methodologies, the underlying molecular and pathobiological characteristics of several malformations of cortical development are being elucidated (Desikan and Barkovich 2016; Holthausen et al. 2016; Holthausen and Blümcke 2016).

**Lateral (or neocortical) temporal origin** is typically characterised by auditory or complex perceptual visual hallucinations, illusions, a dreamy state or vertiginous symptoms. Impairment of consciousness may begin with motor arrest or staring, followed by oroalimentary automatisms. However, automatisms may appear while the patient is still responsive or when consciousness is fluctuating. Amnesia for the ictal event is the rule after alteration of consciousness but may be present even when the patient had apparently remained conscious. According to Blume et al. (1993) and Munari et al. (1994), the

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**Figure 16.16** Left frontal Tayor type focal cortical dysplasia in a 7-year-old boy.
neocortex is responsible for many features of all temporal lobe seizures. Postictal confusion and, in small children, postictal sleep are frequent. Temporal lobe seizures of neocortical origin are less frequent than limbic seizures.

Temporal lobe seizures in children may arise from the basal temporal region rather than mesial temporal structures (Duchowny et al. 1994). Such seizures are marked by behavioural arrest followed by automatisms that begin several seconds after seizure onset. Propagation of mesio-basal seizures is rapid and mainly spreads to the contralateral hippocampus, but may spread to the cingulate gyrus or to orbital and lateral frontal cortex. The concept of temporal ‘plus’ epilepsy was proposed to unify and better individualise specific forms of multilobar epilepsies. Seizures are characterised by electroclinical features primarily suggestive of temporal lobe epilepsy with MRI findings that are either unremarkable or reveal hippocampal sclerosis, and intracranial recordings that reveal seizure origin within a complex epileptogenic network including brain regions within the temporal lobe and neighbouring structures including orbitofrontal cortex, the insulo-opercular region, and the temporo-parieto-occipital junction (Kahane et al. 2015; Barba et al. 2015).

In general, localisation of focal seizures to a particular cortical area is difficult, and distinction between seizures of temporal and frontal lobe origin only on the basis of clinical symptoms may be impossible without intracranial investigation (Manford et al. 1996a).

**Posterior cortex seizures**

Seizures originating from the parietal and occipital lobes (posterior cortex seizures, including the anatomically and functionally adjacent temporal cortex) have a complex semiological presentation. For this reason, localisation based on clinical presentation is difficult and partly explains why they may be under-appreciated, particularly in children.

**Symptoms of ictal involvement of the parietal lobe** may be difficult to diagnose (Salanova et al. 1995a), especially in children, as they are typically subjective and overshadowed by symptoms arising from contiguous central, temporal and occipital cortex. Somatosensory seizures may have a Jacksonian march (Mauguière and Courjon 1978) and are often associated with motor phenomena. Focal seizures arising from the parietal lobe are characterised by positive or negative somatosensory symptoms, rarely pain (Young et al. 1986; Trevathan and Cascino 1988; Ho et al. 1994), or by nausea or an intra-abdominal sensation, illusions of movement or loss of awareness of a part of the body (asomatognosia—especially with non-dominant hemisphere involvement), vertigo or spatial disorientation. Receptive or conductive aphasia (with dominant hemisphere involvement) and postural or rotatory movements may also be seen, and visual symptoms may appear with involvement of the parieto-temporo-occipital junction. Inferior parietal involvement may be accompanied by contralateral or ipsilateral rotatory movements with posturing of the limbs contralateral to the involved hemisphere. Visual illusions, such as macropsia or micropsia or metamorphopsia suggest involvement of the posterior parietal cortex or parieto-temporo-occipital junction.

**Symptoms of occipital lobe** involvement are subjective and may be overshadowed by manifestations resulting from spread to contiguous cortex. Epileptic discharges affecting the primary visual cortex are characterised by elementary visual phenomena, which may be either positive (flashes, phosphenes, rotating colours) or, less frequently, negative (scotomata, hemianopsia, amaurosis). Location is in the hemifield contralateral to the lobe involved. With discharges located more anteriorly, head and eye version is common but not necessarily contralateral. Eye deviation may be periodically interrupted by jerks that return the eyes to the primary position (‘epileptic nystagmus’). Additional manifestations include eyelid flutter.

**Figure 16.17** (a) MRI and (b) FDG-PET of a dysembryoplastic neuroepithelial tumour (DNET) in a 6-year-old girl.
or forced closure of the eyelids and a sensation of eye-pulling (Salanova et al. 1992; Williamson et al. 1992).

In a cohort (Liava et al. 2014) of 62 children undergoing surgery for drug-resistant posterior cortex epilepsy before age 16 years (mean age at epilepsy onset was 3.2 years), 28 children (45%) had onset before age 1 year. Daily seizures were present in 63%. MRI was positive in 58 cases (93.5%) and invasive stereo-EEG (SEEG) was indicated in 24/62 (39%). Surgery was confined to the parietal lobe in 11 children, the occipital lobe in eight, the occipito-parietal region in four, the occipito-temporal region in 18, and involved both the temporal and parietal lobes in the remaining 21. Following surgery, 53 participants (85.5%) were seizure-free. Among patients undergoing SEEG, 75% achieved seizure-freedom. Focal cortical dysplasia was the most frequent histopathological diagnosis (50%), followed by tumoural (24%) and gliotic lesions (14.5%). Older age at epilepsy onset, a restricted epileptogenic area, and complete resection of the epileptogenic zone predicted a favourable surgical outcome.

These results demonstrate that a good surgical outcome is possible in children with drug-resistant posterior cortex epilepsy. Accurate analysis of the chronology of ictal semiology and electrophysiological features, viewed in the context of the complete electroclinical pattern, provides a topographical orientation for posterior cortex epilepsy and, together with the presence of a lesion detectable on imaging, may improve the rate of surgical success of posterior cortex epilepsy in childhood (Francione et al. 2015; Ramantani et al. 2017).

Some Special Epilepsy Syndromes of Lesional Origin

Hypothalamic and Cerebellar Hamartomas; Occipital Epilepsy Associated with Occipital Calcifications

Hypothalamic Hamartoma is a syndrome of gelastic (giggling attacks and/or ‘impression to laugh’) and sometimes dacrystic (crying) seizures of early onset (often in the first year and usually before 2 years of age) is associated with hamartomas of the hypothalamus (Fig. 16.18). The seizures are frequently repeated and highly resistant to treatment (Berkovic et al. 1988; Arzimanoglou et al. 2003; Mullatti 2003; Parvizi et al. 2011; Wilfong and Curry 2015; Kerrigan et al. 2016). Many patients experience cognitive decline and neuropsychiatric comorbidities. Precocious puberty is a frequent feature. The seizure discharge arises from the tumoural core, and surgical excision, although challenging, usually leads to a favourable outcome (Kahane et al. 2003; Kerrigan et al. 2016). Surgical dysconnection or excision yields good results, and several radiosurgery techniques are also used or under evaluation (Fohlen et al. 2003; Polkey 2003a, b; Kerrigan et al. 2016).

Cerebellar hamartomas may produce repeated brief episodes of tonic facial contraction of early onset, similar to the facial hemi-spasm of adults (Al-Shahwan et al. 1996). Harvey et al. (1996) and Arzimanoglou et al. (1999) showed that these may correspond to a typical epileptic EEG discharge within the lesion. AEDs are usually ineffective and polytherapy is not indicated. When possible, surgical resection of the hamartomatous lesion is the most efficacious treatment (Harvey and Arzimanoglou 2016).

Epilepsy related to hypothalamic and cerebellar hamartomas should be evaluated early and referred to specialised referral programmes with clinical and surgical experience.

Abnormalities of cortical development (see Table 16.4) represent the most frequent cause of focal non-idiopathic epilepsies and nearly 40% of drug-resistant cases. This is a rapidly expanding field and a detailed review of these lesional epilepsies is beyond the scope of this chapter. Excellent detailed publications provide an overview of the topic (Guerrini et al. 2003; Blümcke et al. 2011; Kwon et al. 2016; Desikan and Barkovich 2016; Holthausen et al. 2016; Tassi et al. 2016; Barba et al. 2016).

The syndrome of occipital epilepsy associated with uni-or bi-lateral occipital calcifications (Fig. 16.19)
may run a benign course (DeMarco and Lorenzin 1990) or be more severe with secondarily generalised seizures and cognitive deterioration (Gobbi et al. 1988; Tiacci et al. 1993; Gobbi 2005). Such cases are closely reminiscent of Sturge-Weber syndrome (Fig. 16.20) without cutaneous angioma, and similar vascular abnormalities have been reported (Bye et al. 1993) but are inconsistent (Totti et al. 1996). However, there is only minimal or no brain atrophy, and there is no enlargement of the choroid plexus or abnormal deep venous drainage. Most if not all cases of epilepsy with occipital calcification are associated with coeliac disease, and likely to be lesional in nature, although their expression may be reduced to villous atrophy of the intestinal mucosa (Gobbi 2005). The relationship between the coeliac disease and the calcification is not understood.

Occasional and Unusual Epileptic Seizures of Late Childhood and Adolescence

Occasional seizures may rarely occur with acute febrile diseases in older children. They can also occur in a well child or adolescent without fever (Aicardi 1994). Isolated afebrile seizures in adolescents are relatively common. Seizures may be generalised or focal. About half remain single as an isolated cluster lasting less than 36 hours (Loiseau and Louiset 1992; Capovilla et al. 2001). For that reason, treatment of the first afebrile seizure is not recommended unless specific reasons militate for immediate therapy. Isolated convulsions are especially frequent in adolescents during stress and sleep deprivation.

Caraballo et al. (2004) have emphasised that seizures in adolescents usually do not recur when the EEG is normal. This syndrome of partial benign epileptic seizures in teenagers accounted, in their experience, for 24% of all partial seizures beginning in adolescence. The course is benign, but distinction from lesional cases is difficult and neuroimaging studies are required.

Epileptic seizures can disturb all brain functions, and a wide variety of ictal phenomena have been reported, more frequently as isolated case reports. Abdominal epilepsy is characterised by episodes of epigastric or periumbilical pain and/or by repeated episodes of unexplained vomiting. However, epilepsy is rarely the cause of the syndrome of recurrent abdominal pain and periodic vomiting, which is probably more often a manifestation of migraine (Arzimanoglou et al. 2004). In true abdominal epilepsy, loss of consciousness is an important feature.

Seizures limited to vomiting (ictus emeticus) occur rarely (Kramer et al. 1988; Thomas and Zifkin 1999; Shuper and Goldberg-Stern 2004). Other autonomic phenomena that can be the sole or main manifestation of a seizure include cardiac arrest (Kioc et al. 1986; Smaj et al. 1987), ictal arrhythmias (Gilchrist 1985), and apnoea and cyanosis (Southall et al. 1987; Donati et al. 1995; Hewerton et al. 1996). Unusual visual episodes may affect eye movements with ictal gaze deviation or epileptic nystagmus (Thurston et al. 1985) and ictal blindness (Barry et al. 1985). Pain as a seizure phenomenon is rare (Young et al. 1986; Trevathan and Cascino 1988). Shuddering attacks in children were reported by Holmes and Russman (1986), and isolated disturbances of memory (Gallassi et al. 1988) and of sleep with repeated nocturnal awakenings (Peled and Lavie 1986) have also been described.
The precipitation of seizures by specific stimuli occurs in many idiopathic and symptomatic epilepsy syndromes. Also termed ‘reflex epilepsies’, stimulus-evoked seizures are classified as a discrete syndrome only if the patient had solely or predominantly precipitated seizures, which is rare (Wolf et al. 2004; Wolf and Inoué 2005; Koepp et al. 2016). A certain degree of confusion is also due to the fact that the terms ‘provoked’ and ‘triggered’ are sometimes used interchangeably (Pohlmann-Eden et al. 2006). Aird (1983) indicated that 40 seizure-precipitating mechanisms are known. These include tension states, alteration of the level of attention or of consciousness, sleep, psychological factors and hydration state.

With increasing age at onset the complexity of stimuli increases from simple sensory to complex cognitive-emotional. The topography of physiological networks involved follows the posterior-to-anterior trajectory of brain development, reflecting age-related changes in brain excitability. Reflex seizures and traits probably represent the extremes of a continuum, and understanding of their underlying mechanisms might help to elucidate the transition of normal physiological function to paroxysmal epileptic activity (Koepp et al. 2016).

PHOTOSENSITIVE EPILEPSIES

Epileptic seizures triggered by photic (intermittent) stimulation is observed in various epilepsy syndromes and do not constitute a separate entity (Harding and Jeavons 1994). Photosensitivity is especially frequent in adolescents with idiopathic generalised epilepsy (Harding and Jeavons 1994), eyelid myoclonia with absences, and some types of myoclonic epilepsy (Newmark and Penry 1979; Guerrini et al. 1995). Self-provocation is not rare in such patients. The role of television was emphasised by Harding and Jeavons (1994) and Kasteleijn-Nolst Trenité et al. (2002), although other investigators found it limited (Mayr et al. 1987). However, as delivery of the screen image is now digital the provocative role of television viewing is significantly reduced.

Among the factors provoking paroxysmal discharges with analogue television, some seem crucial: the frequency of the television screen refreshment (the 100Hz screen are significantly safer than the 50Hz), the distance from the screen (100cm safer than 50cm), and, particularly for the 50Hz screen, the specific pattern of the images and the act of playing (Badinand-Hubert et al. 1998). Provocation by video games (Maeda et al. 1990; Ferrie et al. 1994; Graf et al. 1994) is also possible but is a reflex rather than a photosensitive epilepsy; computer screens are not associated with photosensitive epilepsy unless the visual image has a flickering or bursting presentation. This problem, as well as that of pattern-sensitive epilepsy, was studied in detail by Harding and Jeavons (1994).

Photosensitive epilepsy is amenable to AED therapy, especially sodium valproate and in some cases levetiracetam. Additional measures in the rare circumstance of analogue television viewing include the use of polarised glasses as well as precautions when watching television; drug therapy is unnecessary if the patient can avoid the stimulus by appropriate measures such as watching television at a distance of 2–3m and wearing dark glasses. Self-induced photogenic or pattern-induced seizures (Harding and Jeavons 1994) are difficult to control. Fenfluramine has been used in such cases together with antiepileptic agents, with some measure of success (Aicardi 1994).

STARTLE EPILEPSY AND MOVEMENT-INDUCED SEIZURES

Startle epilepsy is relatively common in children with early-acquired brain damage (Arzimanoglou et al. 2004). Many patients have congenital hemiparesis but others have diffuse brain dysfunction including Down syndrome. Seizures are usually tonic, involving one or both sides, and follow the startle reaction induced by sudden unexpected stimuli (Chauvel et al. 1992). Sound is often particularly effective but proprioceptive or exteroceptive stimuli can also be the cause and some patients respond electively to particular stimuli. Most cases begin in infancy and many patients have mild to severe intellectual disability. However, Manford et al. (1996b) found that about half the patients with the condition have normal intelligence and a normal neurological profile, and these cases may be associated with cortical dysplasia rather than destructive lesions. Treatment with AEDs is utilised but the occurrence of startle seizures usually implies difficult-to-treat epilepsy. Such seizures should be distinguished from excessive startle disease and from paroxysmal dystonias (see Chapter 19 on Movement Disorders). Touch epilepsy (Ricci et al. 1995) and movement-induced epilepsy are rarer than startle epilepsy.

OTHER ‘REFLEX’ EPILEPSIES

A host of specific stimuli can induce seizures. These include sound, music, and complex and sometimes specific cognitive activities (Wilkins and Lindsay 1985). Eating epilepsy (Fiol et al. 1986) may occur with temporal lobe lesions. Reading epilepsy is a well-defined syndrome but rare in childhood (Wolf 1994; Wolf and Inoué 2005). Seizures induced by immersion in hot water (bathing epilepsy) (Roos and Van Dijk 1988) should be distinguished from syncope (Stephenson 1990), which is probably more common. Other unusual precipitating factors have been reviewed by Wilkins and Lindsay (1985), Aicardi (1994), Arzimanoglou et al. (2004) and Wolf et al. (2004).

The genetic background of reflex seizures and epilepsies is heterogeneous and mostly unknown with no major gene identified in humans (Italiano et al. 2016).
While the cause of epilepsy in approximately one-third of all children with epilepsy remains unknown (van Campen et al. 2013) there is growing recognition that some cases may have an underlying immunological basis. Careful studies of blood, CSF and neural tissue in cryptogenic patients reveal the presence of auto-antibodies to specific neural membrane proteins (Aarli 1980). The first clinical recognition of the potential importance of this mechanism occurred when glutamate receptor antibodies (GluR3) were identified in patients with Rasmussen encephalitis (Rogers et al. 1994). One demonstrated a favourable response to plasma exchange suggesting that this condition was immune-responsive (Vincent et al. 2011). The number of disorders now believed to be immune-related has increased significantly and includes several important clinical disorders (Wright and Vincent 2016). Antibodies associated with neurological disorders and epileptogenesis usually target extracellular loci on neuronal cell membranes and are best identified through assessment of the patient’s immunoglobulin to the native receptor.

**LIMBIC ENCEPHALITIS**

Originally described as a paraneoplastic condition, limbic encephalitis is currently acknowledged to also be an important non-neoplastic entity that is more prevalent and immune-responsive than the neoplastic subtype. Affected patients typically present with cognitive confusion, affective disturbances, amnesia and seizures that primarily involve the temporal lobes. Temporo-medial T2 fluid attenuated inversion recovery (FLAIR) signal abnormalities are common on MRI while histopathological tissue examination reveals lymphocytic-micronodular encephalitis involving mesial temporal structures. A normal MRI is observed in almost half of affected patients and PET may be more sensitive for detection. Temporal hypermetabolism appears early in the course of the illness while hypometabolism occurs later in the course. EEG abnormalities are usually observed in the temporal lobes. Evolution of limbic encephalitis to chronic temporal lobe epilepsy and hippocampal sclerosis is known to occur in adults but has also been described in children (Kröll-Seger et al. 2009). Patients affected with limbic encephalitis share important similarities in clinical presentation but specific auto-antibodies are associated with variation in clinical phenotype.

**Voltage-Gated Potassium Channel (VGKC)-Antibody Receptor Encephalitis**

This entity is the most common form of limbic encephalitis. Most of the antibodies thought to be detected against the VGKC receptors are directed toward other proteins including LG11 (leucine rich glioma inactivated), CASPR2 (contactin associated protein like 2) and contactin.

The onset of VGKC-antibody encephalitis is more prevalent in the adult years where it may present with an acute or subacute onset. Severe permanent amnesia will result unless prompt immunotherapy is provided. Hyponatremia due to inappropriate antidiuretic hormone (ADH) secretion is common while REM sleep abnormalities, autonomic dysfunction, ataxia and neuropathic pain occur more rarely. Seizures of extratemporal origin consisting of limb posturing and facial grimacing have been reported in rare circumstances (Irani et al. 2008). The occurrence of VGLC-antibody receptor encephalitis may be more prevalent in children than previously recognised. A retrospective review of children with encephalitis of unknown origin presenting in status encephalitis detected VGKC antibodies in four out of ten cases as compared to one out of 69 paediatric controls (Suleiman et al. 2011). Testing for infectious causes was negative.

To assess the clinical and immunological findings in children with VGKC, Haochen et al. (2015) retrospectively reviewed the medical records of 39 paediatric patients. They concluded that positive voltage-gated potassium channel-complex antibodies did not indicate a specific clinical syndrome in children but appeared to be a nonspecific marker of neuroinflammatory conditions, particularly encephalopathy. In many paediatric patients, the specific neuronal target remains unidentified in voltage-gated potassium channel-complex-mediated encephalopathy, and it is possible that antibodies bind to intracellular epitopes of the voltage-gated potassium channel-complex and arise secondary to other inflammatory aetiologies (Haochen et al. 2015).

**N-Methyl-D-Aspartate Receptor (NMDAR)-Antibody Encephalitis**

While this disorder occurs in all age groups, it is more common in childhood than VGKC-antibody receptor encephalitis. Onset is typically insidious with gradual deterioration in psychiatric and cognitive functioning as the cardinal presenting signs. Seizures eventually manifest in the majority of cases and sleep disturbances are common. Many patients experience anxiety and agitation during the prodromal period but often progress to coma, autonomic dysfunction, dyskinesia and hypoventilation. Girls are over-represented and may show a different initial clinical presentation from boys who are more likely to present with focal seizures and show a delay in psychiatric symptoms. However, the ultimate clinical evolution and outcomes are similar for both sexes (Viacoz et al. 2014).

A large group of 81 patients with NMDAR encephalitis who were positively identified via referral to a single institution over an 8-month period included 32 children (Florance et al. 2009), eight of whom were diagnosed at a single institution. While ovarian teratomas were found in 56% of women over age 18 years and 31% of girls younger than age 18 years,
no male had a tumour. Paediatric patients ranged in age from 23 months to 18 years. Younger patients had the lowest likelihood of harbouring an underlying tumour. Children were also more likely to evidence more subtle psychiatric signs such as irritability and temper tantrums, and to have subclinical seizure activity. Relapse after treatment occurred in a small proportion of cases.

Glutamate Receptor Epsilon 2 Antibody Encephalitis
This condition is diagnosed by demonstrating antibodies to glutamate receptor epsilon 2 subunits utilising western blotting or recombinant antigen. Despite the antibody response, its immunological target is identified as the NMDAR NR2B subunit expressed in cell lines. While rare, most cases are reported in children (Sakuma 2009). Affected patients typically develop refractory repetitive focal seizures (AERRPS) following an acute infectious process. Most cases either remit spontaneously or are immune treatment-responsive but permanent cortical atrophy and intellectual impairment may occur (Ito et al. 2005).

Glutamic Acid Decarboxylase (GAD) Antibody Encephalitis
The existence of this disorder is somewhat controversial as the target of GAD antibodies is intracellular rather than located on the cell surface. However, apart from limbic encephalitis, GAD antibodies have been identified in other neurological conditions including cerebellar ataxia and stiff-person syndrome (Saiz et al. 2008). Regardless of their significance, GAD antibodies serve as a useful marker of limbic encephalitis. There are now reports of patients with drug-resistant focal epilepsy and anterograde amnesia being diagnosed with this disorder (Mata et al. 2008). Cases of limbic encephalitis with high GAD antibody titres are associated with the development of temporal lobe epilepsy and cognitive disturbance in conjunction with characteristic MRI findings.

Limbic Encephalitis Associated with AMPAR Receptor Encephalitis
This rare disorder occurs primarily in adult women with tumours. It responds well to a combination therapy regimen including tumour and immune suppression but may have a relapsing course. Psychosis has been described (Graus et al. 2010).

Limbic Encephalitis Associated with GABA$_\text{R}$ Antibodies
Seizures are common in this disorder which occurs in patients both with and without tumours. Affected patients respond favourably to immunotherapy (Lancaster et al. 2010).

OUTPATIENT PAEDIATRIC IMMUNE EPILEPSIES
While immune-related mechanisms are increasingly recognised in paediatric patients with non-infectious encephalitis and temporal lobe epilepsy, there is accumulating evidence that immune dysfunction may also play a role in patients with cryptogenic epilepsy without encephalitis. Indeed, this awareness has suggested that a new aetiology of ‘autoimmune epilepsy’ be considered in the evaluation of cryptogenic cases (Quek et al. 2012). The recognition of an immune-related basis has obvious treatment implications particularly as the presence of antibodies has been associated with resistance to AEDs. While it is not yet possible to diagnose immune-related epilepsy on clinical or electrographic criteria, correlational studies hold promise for early recognition and treatment.

Approximately one-sixth of unselected adults with focal epilepsy of unknown cause and with temporal lobe epilepsy and hippocampal sclerosis demonstrate a variety of serum auto-antibodies (Ekizoglu et al. 2014). In comparison to sero-negative controls, patients with positive auto-antibodies evidence significantly higher rates of psychosis and white matter changes on MRI. Affected individuals also show a trend toward higher seizure frequency and AED non-responsiveness. Identified antibodies include GLY-R, CASPR-2, NMDAR and the VGKC complex. Of note, the GLY-R antibody also occurs in patients with progressive encephalomyelitis with rigidity and myoclonus (Hutchinson et al. 2008). The high association of psychosis in this cohort suggests that all patients with focal seizures and psychosis should be screened for the presence of serum auto-antibodies.

Antibodies to neuronal antigens have also been identified in children with new-onset seizures, typically focal seizure disorders (Suleiman et al. 2013b). Eleven of 114 children (9.7%) screened for the presence of serum auto-antibodies to a range of antigens were found to be sero-positive. Auto-antibodies were detected to the VGKC complex, CASPR-2 and NMDAR receptors. A wide variety of epileptic disorders were represented including specific electroclinical syndromes such as Dravet, Lennox–Gastaut and Panayiotopoulos syndromes and BECTS. However, there were no demographic or clinical features that differentiated seropositive from seronegative patients.

TREATMENT OF IMMUNE-MEDIATED SEIZURES
Similar to other CNS disorders involving autoimmune mechanisms, aggressive intravenous corticosteroid therapy and immune globulin are first-line treatments. Plasma exchange has been employed in some patients. Although a favourable response within the first week of treatment occurs in some patients, most do not respond as rapidly. For this reason, medications that cross the blood brain barrier including
Rituximab which targets B cells, and cyclophosphamide have been advocated for resistant patients.

Consensus guidelines and controlled trial data on treatment are lacking but diagnostic and treatment guidelines have been published (Suleiman et al. 2013a; Lim et al. 2015; Graus et al. 2016). These guidelines contain diagnostic criteria for autoimmune encephalitis/epilepsy based on para-clinical and clinical features even without a positive antibody result. This is important (Wright and Vincent 2017) as a recent study demonstrated that some paediatric autoimmune encephalitis patients without neuronal antibodies detected in the serum or CSF can make a significant clinical response to immunotherapy (Hacohen et al. 2013). In the future, it may become possible to target specific antigens to achieve a more optimal outcome.

**STATUS EPILEPTICUS**

Status epilepticus is defined as ‘an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition’ (Gastaut 1973). There are two major categories of status epilepticus: convulsive status (generalised or localised), and non-convulsive, which is subdivided into partial nonconvulsive status and generalised nonconvulsive status (also incorrectly known as ‘petit mal status’). Electrical status epilepticus during slow sleep (ESES) is a separate entity that is included for discussion in this section.

The precise definition of status epilepticus is currently undergoing critical re-examination. In the ‘classic’ definition, status epilepticus is diagnosed whenever there is either continuous seizure activity or recurrent seizures without returning to baseline for at least 30 minutes (Commission 1993). This definition is based on experimental and clinical evidence that continuous seizure activity occurring for this amount of time increases the risk of structural brain damage, particularly hippocampal sclerosis (Van Landingham et al. 1998).

This ‘injury-based’ definition is useful for epidemiological investigation but fails to more narrowly account for the critical stage of evolving status epilepticus whereby inhibitory mechanisms controlling seizure termination are rendered inoperative. While seizures in most children last less than 2 minutes, approximately 25% are more prolonged (Shinnar et al. 2001). The longer the seizure duration, the less likely the seizure will stop within the next few minutes. This recognition suggests a second definition (‘impending’ status epilepticus) in biologically predisposed children, and further indicates that earlier intervention should be instituted, perhaps as early as the 5-minute mark (Shinnar and Hesdorffer 2010). As the median time from seizure onset to arrival in the emergency department is documented to be 33 minutes (Seinfeld et al. 2014) it is imperative that prehospital treatment protocols are established.

A more recent initiative to re-define and re-classify status epilepticus has been undertaken by an ILAE Task Force (Trinka et al. 2015). The Task Force re-examined the concept of status epilepticus with regard to recent evidence suggesting that seizure duration was crucial for its definition. Two time points in seizure development were distinguished – an early one (t1) beyond which a seizure was clinically regarded as being continuous, and a later point (t2) defined as the time point when the risk of structural brain injury increased.

The Task Force further sought to classify status epilepticus on the basis of four clinical axes:

1. Semiology-motor versus non-motor symptoms;
2. Aetiology;
3. Electroencephalography;
4. Age.

In proposing these classification criteria, the Task Force acknowledged that a precise determination is not always possible, particularly at first presentation. The practical advantages of this novel classification schema were also not specified.

**CONVULSIVE STATUS EPILEPTICUS**

**TONIC–CLONIC STATUS EPILEPTICUS**

Convulsive tonic–clonic status epilepticus may present as a succession of tonic–clonic seizures without recovery of consciousness between individual episodes or as a single, prolonged convulsive seizure, most often of a purely clonic type. The duration necessary to diagnose convulsive status epilepticus is variably estimated (Shorvon 1994; DeLorenzo et al. 1999; Lowenstein et al. 1999; Trinka et al. 2015). The difficulties for a universally accepted definition based on duration derive directly from the fact that in everyday clinical practice, a treatment is applied to all seizures lasting longer than 5 or 10 minutes, while changes in metabolism and vital functions usually appear after 30 minutes. If a duration component is included in the definition of status – to evaluate new drugs or for epidemiological studies – this should be the minimum duration (5 minutes) after which medical care is usually applied (Arzimanoglou et al. 2004; Trinka et al. 2015). Care should be taken to exclude the postictal period. Lowenstein et al. (1999) discussed the need for a revised, more operational, definition of status epilepticus. The findings by Theodore et al. (1994), who evaluated the overall duration of the convulsive part of a ‘typical’ isolated seizure as being slightly more than 1 minute and rarely in excess of 2 minutes, support the operational definition for status proposed by Lowenstein et al. (1999).

Exclusively or predominantly unilateral seizures are more common in childhood than bilateral convulsive status.
(Aicardi and Chevrie 1983). In most patients, clonic jerks may wax and wane in intensity and the involved territory may vary from moment to moment as does the rhythm of the jerks, which, generally, are not synchronous in the affected segments.

Convulsive status epilepticus is often preceded by a premonitory stage of serial seizures, during which treatment is particularly effective (Shorvon 1994; Pellock et al. 2004). Established convulsive status can be divided into an early or compensated stage during which physiological mechanisms are sufficient to meet the metabolic demands and cerebral tissue is protected from hypoxic or metabolic damage, and a stage of decompensation when compensatory mechanisms break down and brain damage may occur. As the duration of status increases, the clinical seizures often become less conspicuous, eventually evolving into unresponsiveness with minimal jerks or without visible movements, while autonomic changes become more prominent with resulting respiratory and circulatory impairment, often associated with hypothermia.

The EEG features of convulsive status epilepticus are variable. Generalised paroxysmal activity, as described in adults (Treiman 1993; Shorvon 1994), is less common in children than asymmetrical slow waves irregularly interspersed by spikes and sharp waves. In cases of prolonged status epilepticus, episodes of ‘flattening’ of the EEG frequently occur. Periodic generalised or lateralised epileptiform discharges may be seen in very long episodes and indicate a poor prognosis (Garg et al. 1995).

The term focal or partial convulsive status epilepticus (see below) applies only to those cases in which convulsive activity remains localised to a restricted segment on one side of the body without generalisation or diffusion to the whole of the affected side. When segmental myoclonic jerks are continuous, the condition is known as epilepsy partialis continua. In such instances, intermittent somatomotor seizures may start from the area of the body that is involved by permanent myoclonus; this association defines the Kojewnikow syndrome.

Convulsive status epilepticus is a major complication of epilepsy and remains a dangerous condition, even though its prognosis has improved in past decades. The pathogenesis of convulsive status epilepticus and of its consequences has been extensively studied (see Brown and Hussain 1991a; Shorvon 1994; Wasterlain and Treiman 2006). It involves multiple factors that include progressive hypoxia, substrate failure, ATP depletion and intracellular acidosis. These, in turn, eventually produce a fall in cardiac output, hyperkalaemia, metabolic acidosis and cerebral oedema, all of which produce sequelae, but fortunately only rarely appear when convulsive status lasts less than 90–120 minutes (Aicardi and Chevrie 1983).

The role of excitotoxicity due to excessive activation of the excitatory neurotransmitters, especially glutamate (glutamate cascade), with consequent massive influx of Ca++ ions in neurons leading to apoptosis or cell necrosis is now considered to be the primary deleterious phenomenon. Blocking this excitotoxic cascade may be important for neuroprotection (see corresponding chapters in Wasterlain and Treiman 2006).

Systemic factors also play an important role in the production of sequelae. However, it seems that the epileptic activity itself, in the absence of systemic complications, can generate brain lesions, especially in the temporal lobe (Holmes 2002; Lado et al. 2002; Wasterlain and Treiman 2006), probably at least in part by a mechanism of glutamate-induced excitotoxic damage.

The incidence of convulsive status epilepticus ranges from 3% to 16% of all patients with epilepsy (Hauser 1994; Wu et al. 2006) in childhood series of epilepsy. Contrary to adults, status is often the first epileptic presentation in infants and children. This was found in 77% of the 239 patients in the Aicardi and Chevrier (1970) historical series. Similarly, 24% of all children with a first afebrile seizure before the age of 10 years in Minneapolis (Hauser 1983), presented with convulsive status epilepticus. Convulsive status epilepticus is especially common in the first 2 years of life, and approximately 75–85% of cases occur before the age of 5 years (Aicardi and Chevrier 1970). After age 3 years, the annual frequency remains stable at around 3–5% until age 15 (Aicardi and Chevrier 1970).

The overall incidence of convulsive status epilepticus has not declined. A prospective population-based study performed by the North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) group enrolled 226 children, 176 of whom had had a first ever episode of convulsive status epilepticus (Chin et al. 2006). Ninety-eight children (56%) were neurologically healthy before their first episode, and 56 (57%) of those children experienced a prolonged febrile seizure. Eleven (12%) children with their first febrile convulsive status epilepticus had acute bacterial meningitis. A conservative estimation of 1-year recurrence of convulsive status epilepticus was 16% (10–24%). Case fatality was 3% (2–7%).

Convulsive status epilepticus can be symptomatic, resulting from underlying CNS diseases that may be acute, such as trauma, vascular collapse, electrolyte disorders, meningitis or encephalitis, or progressive such as brain tumours or progressive encephalopathies; remote symptomatic, due to chronic nonprogressive brain lesions such as glial scars or late sequelae of infectious or anoxic events; or cryptogenic, occurring at the onset of the epilepsy or in the course of a recurring seizure disorder (Hauser 1993). In this case, interruption of treatment is often a precipitating event. It may also represent an occasional seizure, in practice mostly a febrile seizure that fails to stop for unknown reasons. Such cases differ from common febrile seizures only in duration, not in nature.

Knowledge about the aetiology potentially underlying status epilepticus may help to guide diagnostics and eventually influence treatment decisions. Some epilepsy syndromes engender a very low risk of convulsive status epilepticus (Bast 2014) while it is much higher in others (Neubauer and Hahn 2014). Currently, it appears that a large majority of cases of status observed in industrialised countries are of symptomatic origin especially in infants. The dramatic decrease in the frequency of cryptogenic status probably results in large part from a better and more prompt treatment of epilepsy and
of incipient febrile status. The improved outlook for status should not lead to underestimation of the potential risks or failure to instigate immediate vigorous therapy.

In a prospective cohort of 1382 children with convulsive status epilepticus, average age at onset was 3.4 years and seizure duration ranged between 21 and 60 minutes (Singh et al. 2010). The most common presentation was a cryptogenic febrile convulsion. The most common acute precipitating event was CNS infection while cortical malformation was the most common remote symptomatic aetiology. Neuroimaging studies provided a diagnosis in only 30% of cases. Continuous EEG provided evidence of nonconvulsive status in five patients (4%) underscoring the important role of continuous EEG monitoring in all children presenting with status epilepticus.

A once common syndrome of convulsive status epilepticus is the hemi-convulsion–hemiplegia or H–H syndrome (Gastaut et al. 1960; Arzimanoglou and Dravet 2003), characterised by the occurrence, in the course of a febrile disease in a child of less than 4 years of age, of prolonged clonic seizures with a marked unilateral predominance. This phase is followed by long-lasting hemiplegia, and after 1 to several years, partial epilepsy, with seizures originating in the hemisphere contralateral to the hemiplegia (hemi-convulsion–hemiplegia–epilepsy or HHE syndrome); 85% of affected children are intellectually deficient. Computed tomography (CT) and MRI are characteristic showing initial oedematous swelling in one hemisphere followed by global atrophy independent of any vascular territory (Fig. 16.21). The incidence of the syndrome has declined considerably over the past 20 years in industrialised countries, probably because of prompt treatment with benzodiazepines; however, cases are still frequent in developing countries.

**Outcome of Tonic–Clonic Status Epilepticus**

The quality of available studies on the outcome of convulsive status epilepticus is influenced by a number of factors: prospective or retrospective; population-based or hospital-based; duration of follow-up, short-term versus long-term outcome; aetiological groups considered; and definition of variables, particularly those related to morbidity issues. In an excellent methodological review (Raspall-Chaure et al. 2006) of 1727 potentially eligible studies, only 63 met the criteria for entry into the review. Population-based studies scored better than hospital-based ones.

The outcome of convulsive status epilepticus has improved considerably over the past four decades. Aicardi and Chevrie (1970) found a mortality rate of 11% in a series of 239 children younger than 15 years. More recently, long-term mortality after a first episode of afebrile status was evaluated in a population-based retrospective cohort study in the Rochester Epidemiology Project Records (Logroscino et al. 2002). In this study, 19 patients (13%) were aged below 1 year, and 35 (24%) were between the ages of 1 and 19 years. At 10 years, the cumulative mortality among 30-day survivors was 43% (62 deaths); mortality among patients 65 years and older was 76%, but in the under 1 year and 1–19 year age groups, respectively, it was only 5% and 2%.

Case fatality for first ever episodes of convulsive status epilepticus was 3% in the NLSTEPSS prospective, population-based study of convulsive status epilepticus in childhood (Chin et al. 2006). Three children had acute bacterial meningitis, one had glutaric aciduria Type I, and three had progressive neurodegenerative disorders that, despite investigation, did not have syndromic diagnoses. The most common cause of convulsive status epilepticus in this series was a prolonged febrile seizure, which is probably associated with low morbidity and mortality. In a subgroup analysis of 95 children with first ever episodes of convulsive status epilepticus associated with fever (temperature >38°C at presentation), 11 children (12%, 95% confidence intervals 6–18%) had acute bacterial meningitis and seven (8%, 95% confidence intervals 2–13%) had a viral CNS infection. The remaining children had either prolonged febrile seizures (n=56, 59%) or a previous neurological abnormality with a febrile intercurrent illness (n=21, 22%).

According to the Raspall-Chaure et al. (2006) systematic review, short-term mortality after convulsive status epilepticus is 2.7–5.2% if studies with the highest quality scores are considered. If only children admitted to ICU are included, mortality is estimated at between 5% and 8%.
Mortality rates in children have decreased, probably due to earlier administration of benzodiazepines treatment and better intensive care facilities. Most paediatric deaths occur between the ages of 1 and 4 years with underlying aetiology being the main determinant; death during status is typically associated with respiratory or cardiac arrest. Mortality rates are higher for acute symptomatic status epilepticus in new neurological conditions (encephalitis, trauma) as compared to convulsive status epilepticus in relation to a first seizure in idiopathic epilepsy or febrile status epilepticus.

Long-term complications include secondary epilepsy, cognitive deterioration of variable degree, behavioural problems and focal neurological deficits. Available figures are difficult to interpret because the sequelae may represent complications of the underlying condition rather than the status itself, or they may have antedated the convulsive episode. Neurocognitive assessment is often not available and eventual sequelae are not always reported. Cognitive and neurological deficits are often comorbid with the epilepsy. Quality of the studies and study design are also important determinants. When considering only the highest-scored studies, neurological sequelae are reported in fewer than 15% of children. Rates as high as 50% are reported in younger children, an age range with a higher incidence of acute symptomatic convulsive status epilepticus.

In the classic series of Aicardi and Chevrie (1970), epilepsy persisted after the episode of status in 44% of children, compared with an incidence of 23% with epilepsy before the status. Outcome in symptomatic cases is significantly poorer than in cryptogenic cases. Other unfavourable factors include younger age and longer duration of convulsive status. The proportion of cases with neurological or cognitive sequelae has been considerably reduced in more recent series. The incidence of H–H syndrome, which was once common, has decreased in industrialised countries. However, hippocampal sclerosis may develop after an episode of status. Longitudinal studies of cohorts with prolonged febrile seizures (see FEBSSTAT studies in the Febrile Convulsions section) will allow a more comprehensive characterisation of outcomes.

The risk of recurrent status following a first episode of convulsive status epilepticus has also decreased. Recurrence is more frequent in cases with an underlying chronic or degenerative neurological condition. According to Shinnar et al. (1997), new episodes occur mainly in symptomatic cases and in children with abnormal neurological signs that predate the first status; these latter children account for 88% of the recurrences. Idiopathic or febrile status epilepticus in typically developing children is largely an isolated event. The recurrence risk for convulsive status in idiopathic cases was only 4% for initial idiopathic status and 3% for febrile status, but this increased to 11% for cases of acute symptomatic status and to 44% for remote symptomatic cases. In the NLSTEPSS study (Chin et al. 2006) a substantial proportion (16%) of children with first ever convulsive status epilepticus had a recurrence within a year, and those with a previous neurological abnormality were more likely to have a recurrence ($P=0.04$).

**Treatment of Tonic–Clonic Status Epilepticus**

The treatment of convulsive status epilepticus in hospital is summarised in Table 16.14 (see also Brown and Hussain 1991b; Shorvon 1994; Arzimanoglu et al. 2004; Treiman and Walker 2006; Wasterlain and Treiman 2006).

Treatment is indicated in all cases after exclusion of pseudo-status epilepticus. The two objectives of treatment are to quickly stop seizure activity and to maintain adequate respiratory, cardiovascular and metabolic functions. Clearly, the prevention of respiratory and circulatory complications has a major role in the prevention of residual damage. There is, however, experimental and clinical evidence that convulsive activity alone is probably harmful. Efforts should therefore be made to arrest the status before systemic signs intervene (see evolution of the concepts in reviews by Meldrum 1978; Aicardi and Chevrie 1983; Brown and Hussain 1991a; Wasterlain and Treiman 2006). Prompt intervention is imperative because the outcome is related to the duration of the convulsive event and because therapy becomes progressively less efficacious and more hazardous the longer the seizures continue (Shorvon 1994; Chin et al. 2006).

In the premonitory and early phases of serial seizures and incipient status (usually outside the hospital) emergency treatment is based on intravenous, rectal, buccal or nasal administration of benzodiazepines. In a prospective randomised study (Lahat et al. 2000), seizures were controlled more quickly with intravenous diazepam than with intranasal midazolam, although midazolam was as safe and effective. The overall time to cessation of seizures after arrival at hospital was faster with intranasal midazolam than with intravenous diazepam.

In another prospective randomised trial (McIntyre et al. 2005), buccal midazolam was more effective than rectal diazepam for children presenting to hospital with acute seizures and was not associated with an increased incidence of respiratory depression. Chamberlain et al. (1997) reported that intramuscular midazolam was an effective anticonvulsant for children with motor seizures. Compared to intravenous diazepam, intramuscular midazolam resulted in more rapid cessation of seizures because of more rapid administration. Intravenous lorazepam has a more prolonged effect and may be equal or superior to phenytoin (Treiman and Walker 2006).

Dieckmann (1994) and Alldredge et al. (1995) have added evidence that prehospital treatment reduces significantly both the duration of seizures and the likelihood of recurrent seizures in the emergency department, and is reasonably safe. They did not encounter respiratory depression that has led other authors (e.g. Phillips and Shanahan 1989) to advise against emergency benzodiazepine treatment.

Recent availability of easier to administer rescue drugs (buccal or nasal midazolam versus rectal diazepam) could modify clinical practice. However, the first need today remains to establish the acceptance of available therapies among those
treating children (Arzimanoglou et al. 2014). Rescue medication unavoidably involves parents, family friends and schoolteachers. Results of a health care providers survey have identified several clear gaps that need to be addressed: clearer guidance that spans all settings of care, greater dissemination of such guidelines across the chain of care, more open communication and better links between health care providers and schools, and systematic training of all relevant caregivers on the appropriate management of prolonged convulsive seizures (Arzimanoglou et al. 2014). Currently available evidence allows us to confidently prescribe available rescue drugs when indicated. Once a child is identified as being at risk, time for rescue administration must be determined on an individual basis. The ’5 minutes’ represent a reasonable, and easy to
teach, reference frame. The treating physician, who will also have to consider the habitual duration of seizures of a patient, can then adapt it and appropriately advise the caregivers (Arzimanoglou and Lagae 2013).

During convulsive status epilepticus the patient should be placed in the lateral prone position and the airway cleared. During transportation, the same position should be maintained. In the hospital, ICU treatment is preferable. Maintenance of adequate oxygenation and circulation is clearly essential. Hypoxia is usually more severe than anticipated on clinical grounds, and ventilatory support should not be delayed. Pressor therapy (dopamine) is often necessary in protracted status. Any hypoglycaemia, acidosis and electrolyte disorders should be corrected. Regular monitoring, including

<table>
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<th>Table 16.14 Management of convulsive status epilepticus*</th>
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| **Immediate management**
| (1) Assessment of vital functions
| (2) Administration of a benzodiazepine (may repeat dose once):
| Intravenous diazepam (0.25–0.5mg/kg, not faster than 2mg/min) OR
| Intravenous lorazepam* (0.1mg/kg/dose; max. 4mg/dose; over 2–5 mins) OR
| Intramuscular midazolam (10mg for >40kg, 5mg for 13–40kg, single dose)
| Buccal administration of midazolam or rectal administration of diazepam (0.5–1.0mg/kg) may be used if intravenous line is not established
| **Second stage** (within 5–30 minutes from onset)
| Steps 3–4 in all patients
| (3) Monitoring of vital functions and correction of disturbances. ECG. Tracheal intubation if necessary
| (4) Investigations of the possible cause of status, especially metabolic and infectious (lumbar puncture may be required)
| (5) Intravenous administration of 100mg pyridoxine (for under 2 years of age)
| (6) Other treatment of cause if available (meningitis, encephalitis)
| Steps 7–8 if seizures are not controlled within minutes of giving benzodiazepines
| (7) Repeat dose of a benzodiazepine may be given but preferably pass on to one of the options of step 8
| (8) Administration of second therapy of choice (no evidence base)
| Intravenous phenytoin (loading dose 20mg/kg to obtain a serum level of 20–25µg/mL, not faster than 25mg/min) or
| intravenous fosphenytoin (20mg PE/kg, max: 1500mg PE/dose, single dose); OR
| Intravenous levetiracetam (60mg/kg, max: 4500mg/dose, single dose); OR
| Intravenous valproic acid (40mg/kg, max: 3000mg/dose, single dose); OR
| Intravenous phenobarbitone (loading dose 15–20mg/kg) (some clinicians advise larger doses up to 100mg/kg in intractable cases, if respiratory support available)
| Steps 9–11 for resistant status (40–60 minutes from onset)
| (9) Close EEG monitoring and supervision by specialised medical and nursing personnel (ICU)
| (10) No clear evidence to guide order of choices
| Repeat second-line therapy (Step 8) OR
| Anaesthetic doses of either thiopental, midazolam, phenobarbital or propofol
| Neuromuscular blockade may be necessary for maintaining ventilation. EEG monitoring is imperative

*See also Glauzer et al. (2015).

Families and caregivers of children with epilepsy known to be at risk of convulsive status epilepticus (or serial seizures) should be educated on how to administer either buccal midazolam or rectal diazepam early (pre-hospital setting), in situations of unusually prolonged seizures.

*Lorazepam has a longer half-life than diazepam and no long-life metabolite. It may be less of a respiratory depressant than diazepam, especially in patients who have previously received phenobarbitone.
if necessary oximetry, central venous pressure and, if possible, continuous EEG, should be established and a rapid search for an underlying cause should be performed following immediate anticonvulsant drug administration. The possibility of pleocytosis due to status epilepticus should be kept in mind when meningitis is suspected. Transient CT and MRI changes (Henry et al. 1994) resulting from convulsive activity can wrongly suggest a lesional cause.

For detailed information on drug treatment, the reader is referred to Shorvon (1994) and Wasterlain and Treiman (2006). Overtreatment is dangerous as anticonvulsant drugs in high doses can induce respiratory depression and hypotension. Maintenance treatment should, therefore, be substituted for acute therapy as soon as possible. In exceptional cases (Gorman et al. 1992; Alexopoulos et al. 2005; Schrader et al. 2013; Oderiz et al. 2015) and for rather specific aetiologies neurosurgical treatment has been used successfully.

**GENERALISED TONIC STATUS EPILEPTICUS**

Generalised tonic status, although it is a form of convulsive status epilepticus, will be studied with nonconvulsive status epilepticus with which it is often associated and shares aetiological factors.

**MYOCLONIC STATUS EPILEPTICUS**

Myoclonic status epilepticus may be observed following hypoxia due to cardiac arrest (Shorvon 1994) or in the late stage of convulsive status (Treiman 1993). A subtype form occurs in children with congenital nonprogressive encephalopathies (Dalla Bernardina et al. 1992) or with Angelman syndrome (see Chapter AA to supply). Some myoclonic activity, usually erratic in type, is common in nonconvulsive status epilepticus.

**PARTIAL CONVULSIVE STATUS EPILEPTICUS (RASMUSSEN ENCEPHALITIS)**

Partial convulsive status epilepticus (epilepsia partialis continua) may be a feature of localised static brain damage involving the motor strip. Focal dysplasia (Kuzniecky et al. 1988; Kuzniecky and Powers 1993) and hemimegalencephaly (Fusco et al. 1992) are common causes but destructive lesions are sometimes encountered (Cockerell et al. 1996). Epilepsia partialis continua may also be a feature of progressive conditions, including indolent tumours, strokes associated with mitochondrial diseases (Chevrie et al. 1987; Antozzi et al. 1995), subacute meases encephalitis in immunosuppressed children (Chapter 11) and Alpers poliodystrophy (Chapter 10). Marked hyperglycaemia without ketosis may cause focal status in adults. A similar syndrome of focal spinal myoclonus with extreme hyperglycorrhachia due to accidental dislocation of a venous catheter into a perispinal vein has been reported in a neonate (Bass and Lewis 1995).

A frequent cause of focal convulsive status epilepticus is Rasmussen encephalitis (Rasmussen and Andermann 1989; Hart 2004), a slowly progressive disease that involves exclusively or predominantly one hemisphere, especially the frontotemporal region. Focal seizures are the first symptom and epilepsy partialis continua develops at some stage in over half the patients. Progressive hemiplegia, aphasia, hemianopia and intellectual deterioration become apparent after months or years of seizure activity. The EEG shows diffuse paroxysmal activity and a slow background tracing over the involved hemisphere. Neuroimaging shows progressive atrophy that usually begins in the frontotemporal area and later spreads to the whole hemisphere and occasionally to the opposite side.

Advances in neuroimaging suggest that progression of the inflammatory process seen with MRI might be a good biomarker in Rasmussen encephalitis. Pathologically, perivascular cuffing and glial nodules are present in areas of neuronal loss and glial proliferation (Vinters and Wasterlain 1996). The disorder may be associated with the presence of antibodies to the R3 glutamate receptors. Although these have been shown experimentally to be capable of stimulating the receptors and might thus be a cause of the epilepsy, their role seems limited. AED treatment of the disorder is often ineffective and surgery is often necessary (Hart 2004). Only large resections (hemispherectomy) are effective in the majority of cases (Andermann et al. 1992; Vining et al. 1993, 1997).

Long-term outcome after surgery was reported in 23 patients with Rasmussen encephalitis by a Brazilian epilepsy team (Terra-Bustamante et al. 2009). In this retrospective study patients were divided into two groups: fast evolution and slow evolution to hemiparesis and epilepsy partialis continua. According to the authors these groups may represent different Rasmussen encephalitis substrates. Fourteen patients achieved satisfactory seizure control, three had a partial response to surgery, and five were unchanged. All patients with left-side involvement presented with language disturbance that did not improve after surgery in 66.6% of patients. Cognitive evaluation showed that the majority of the patients did not have any significant improvement, and 38.1% had cognitive deterioration after surgery. For many patients, families, and doctors, choosing the right time to undertake surgery is a therapeutic dilemma (Varadkar et al. 2014). Decisions of whether or when surgery should be undertaken are challenging in the absence of a dense neurological deficit, and vary by institutional experience. Further, the optimum time for surgery, to give the best language and cognitive outcome, is not yet well understood.

Corticosteroid and immunoglobulin treatment can be partly effective (Chinchilla et al. 1994; Hart et al. 1994) but seem only to slow rather than halt disease progression in Rasmussen encephalitis, without changing the eventual outcome (Varadkar et al. 2014). Encouraging preliminary results of plasmapheresis (Prasad et al. 1996) have not been confirmed or are transient. The disorder appears less severe in adolescents (Hart et al. 1997). A study in 13 patients demonstrated that most of the brain injury occurs during the
first 8–12 months of the disease (Bien et al. 2002). A viral infection has been proposed, and both cytomegalovirus and Epstein–Barr virus have been suspected without definite proof. Herpes simplex virus Type 2 has been reported as the cause of smouldering encephalitis with temporal lobe epilepsy in two adult patients with many features reminiscent of Rasmussen syndrome (Cornford and McCormick 1997).

A European Consensus Statement on formal diagnostic criteria and a treatment algorithm was published in 2005 (Bien et al. 2005).

**NONCONVULSIVE STATUS EPILEPTICUS**

Nonconvulsive status epilepticus almost always occurs in children with known epilepsy (Porter and Penry 1983; Shorvon 1994). It may belong to several epilepsy syndromes. A clear-cut differentiation, on clinical and even electroclinical grounds, between generalised and partial nonconvulsive status epilepticus is difficult and often arbitrary (Arzimanoglou et al. 2004; Sutter and Kaplan 2012). The definition depends upon the criteria to be applied (type of seizures and/or type of epilepsy and/or characteristics of EEG abnormalities and/or aetiology). Beniczky et al. (2013) proposed a unified terminology and classification system for NCSE, using, as a template, the standardised computer-based organised reporting of EEG (SCORE). This approach integrates the terminology recently proposed for the rhythmic and periodic patterns in critically ill patients, the electroclinical classification of NCSE (type of NCSE) and the context for the pathologic conditions and age-related epilepsy syndromes.

**GENERALISED NONCONVULSIVE STATUS EPILEPTICUS (RING CHROMOSOME 20)**

Generalised nonconvulsive status epilepticus may occur following an initial convulsive seizure (Cascino 1993) or can culminate in a generalised convulsion. It is characterised clinically by variable degrees of clouding of cognitive processes, from simple slowing of ideation to complete unconsciousness, and electrically by bilateral discharges of spike–wave complexes. Various terms have been used in the literature (absence status, petit mal status, spike–wave stupor, epilepsy minoris continua, or epileptic twilight state), none being entirely satisfactory.

Two subgroups are recognised, although their clinical and even electroclinical differentiation is not always evident. Typical absence status occurs in the course of idiopathic generalised epilepsy; atypical absence status occurs largely in secondarily generalised epilepsies, specifically in Lennox–Gastaut and Dravet syndromes and some of the myoclonic epilepsies, including the spectrum of epilepsies with predominantly myoclonic–astatic seizures. They are difficult to differentiate as the EEG discharge is infrequently of a classic, regular, 3Hz type reminiscent of typical absences, and in many cases the spike–wave discharge is broken up into frequent bursts, is arrhythmic in frequency or is of less than 3Hz (Cascino et al. 1993). Consciousness is variably impaired from a simple slowing of ideation and expression to profound obtundation or lethargy (Shorvon 1994).

Patients with the Lennox–Gastaut syndrome frequently have prolonged episodes of diminished consciousness, often associated with erratic myoclonus and/or brief head drops due to localised muscle atonia or myoclonic jerks. These episodes are sometimes accompanied by an increase in abnormal EEG activity, but it may be difficult to distinguish between ictal and non-ictal states (Erba and Browne 1983). Thus, such cases are often excluded from nonconvulsive status. Repeated tonic seizures often interrupt such episodes or may replace them, a transition that is sometimes produced by the use of benzodiazepines (Alvarez et al. 1981; Di Mario and Clancy 1988).

Another nosological issue is raised by the occurrence of episodes of status identical to those observed in primary or secondary generalised epilepsies in children with focal epilepsies as evidenced by the occurrence of focal seizures, discrete EEG foci, and localised lesions. In such cases, paroxysmal EEG activity during status is bilateral, although at times asymmetrical, and it is difficult to decide whether they should be classified under partial or generalised nonconvulsive status (Arzimanoglou et al. 2004).

**Absence status** occurs before age 20 in 75% of cases, mostly during the first decade, and is rarely the first manifestation of epilepsy. A form of ‘de novo’ absence status of late onset has been described in middle-aged and elderly patients, usually related to benzodiazepine withdrawal (Thomas et al. 1992). The outcome of absence status is probably related more to the type and cause of the underlying epilepsy than to the duration of repetition of the episodes. The role of sub-continuous EEG paroxysmal activity, with few or even no clinical manifestations, as a cause of cognitive or behavioural deterioration in several epilepsy syndromes, remains debatable.

The diagnosis of generalised nonconvulsive status is often challenging. Intoxications must be considered with unexplained obtundation; coma or confusion of metabolic origin common in children.

Episodes of pure **tonic status** are frequent in Lennox–Gastaut and related syndromes. They may last several days or weeks, the individual seizures becoming shorter and less intense, while autonomic impairment increases with the duration of status.

**Atonic status** is characterised by the occurrence of near-repetitive brief losses of tone (negative myoclonus) involving axial and limb musculature. Diminished consciousness is typically associated, and erratic myoclonic jerks are often present. Such episodes, lasting hours or days, frequently complicate the course of myoclonic (myoclonic–astatic) epilepsy but may also occur with focal epilepsy, lesional or...
nonlesional. Episodes of myoclonic or atypical absence status epilepticus occur in the majority of cases with Angelman syndrome (Battaglia and Guerrini 2005).

A specific epilepsy syndrome, associated with the ring chromosome 20, has been described (Inoue et al. 1997; Petit et al. 1999; Ville et al. 2006) as a recognisable entity with almost daily episodes of atypical absence status. The syndrome is characterised by mild to moderate intellectual disability, presenting around age 6 years after initially normal development, a behavioural disorder, the lack of specific dysmorphic features and epilepsy. Seizures usually begin in childhood, and are reported as a fluctuating alteration of awareness lasting several minutes. These may be associated with automatic behaviour, wandering hallucinations, and a sensation of fear. Brief motor seizures and tonic–clonic seizures are also observed. The ictal EEG during nonconvulsive status reveals high-amplitude rhythmic slow activity with superimposed spikes or spike–waves over the frontal regions.

The importance of EEG monitoring and aggressively treating nonconvulsive status epilepticus is underscored by a recent prospective observational study of 300 critically ill children with encephalopathy (Wagenman et al. 2014). All children underwent continuous EEG monitoring to determine the relationship of electrographic seizures and electrographic status epilepticus and long-term neurological outcome. Follow-up at a mean of 2.7 years revealed that nonconvulsive status epilepticus but not electrographic seizures was associated with lower cognitive performance and diminished quality of life. Children with no prior history of seizures were at increased risk of subsequently being diagnosed with epilepsy.

Treatment of generalised nonconvulsive status epilepticus with benzodiazepines (diazepam, midazolam, clonazepam or lorazepam) usually rapidly controls primary generalised episodes. Valproate is used to treat absence or myoclonic status (Aldenkamp et al. 2006). Atypical absence status, however, is often resistant to drugs. High doses are best avoided, and benzodiazepine administration must be immediately interrupted if tonic components become apparent. Tonic status is highly resistant to therapy (Livingston and Brown 1987). Dexamethasone may be helpful (Shorvon 1994).

PARTIAL NONCONVULSIVE STATUS EPILEPTICUS

Partial nonconvulsive status, rare in children, can occur in the course of temporal lobe or other lesional epilepsies, particularly involving the frontal lobe. It may present as frequently recurring focal seizures with alteration of consciousness and automatisms without full recovery of cognitive activity between seizures, or as continuous long-lasting episodes of cognitive confusion and/or behavioural disturbances with or without automatisms (Arzimanoglou et al. 2004). An alternation of periods of complete unconsciousness and of partial responsiveness is possible. The differential diagnosis with generalised nonconvulsive status depends on the EEG which shows permanent or repetitive localised paroxysmal activity, although with variable localisation (McBride et al. 1981; Bauer et al. 1989). Lasting postictal memory deficits are described in adults (Shorvon 1994).

Depending on the location and propagation of the discharges, partial nonconvulsive status may also manifest as episodes of prolonged unmitted fear, prolonged aphasia, prolonged ictal blindness (status epilepticus amnesticus) or visual hallucinations. Prolonged ictal paralysis (somato-inhibitory status) is another form of nonconvulsive status that may be difficult to distinguish from Todd paresis. Nonconvulsive status may also take the form of a prolonged ‘aura’, characterised by prolonged visceral or sensory symptoms. Among other lesional causes cortical dysplasia may explain many prolonged episodes. Therapeutic options to control partial nonconvulsive status epilepticus do not differ from that of status in general. However, the urgency of administration and the choice of medication may be unclear. Data addressing treatment of convulsive status epilepticus may lead to ‘overtreatment’ of nonconvulsive status as sedating medications may prolong hospitalisation and worsen outcome. Non-sedating antiepileptic drug use is favoured by many neurologists as their side effect profile is superior to sedating medications (Wasim and Husain 2015).

REFRACTORY STATUS EPILEPTICUS

Refractory status epilepticus (RSE) is defined as status epilepticus that does not respond to the administration of conventional antiepileptic medications (Shorvon and Ferlisi 2011). This clinical situation is not rare and occurs in up to one-quarter of patients presenting in status epilepticus. Morbidity and mortality are particularly high given the long periods of continuous seizure duration (Novy et al. 2010). It is therefore important to document medication unresponsiveness as early as possible.

Whereas convulsive status epilepticus does not generally present difficulties in diagnosis, nonconvulsive status epilepticus may be overlooked, particularly in comatose patients. For this reason, continuous EEG monitoring in the intensive care setting is mandatory. Persistence of nonconvulsive status epilepticus in patients successfully treated for convulsive status epilepticus is not uncommon. Cases of RSE that continue 24 hours or more have been termed ‘super-refractory status epilepticus’ (Shorvon and Ferlisi 2010). While constituting a small percentage of RSE patients, this group is at extremely high risk for poor outcome.

Patients with RSE must be managed in an intensive care setting as anaesthetic agents are typically employed and a variable degree of coma is generally achieved. Once first and second-line anti-seizure medications have failed, coma should require intervention.
be induced with midazolam, thiopental sodium or propofol (Capovilla et al. 2013). The choice of anaesthetic agent is typically dictated by local protocol. Each agent carries individual risks. Induction of thiopental is associated with hypotension and heart failure and is contra-indicated in the presence of cardiogenic shock or sepsis. Intravenous propofol in high doses for prolonged periods is associated with the ‘propofol infusion syndrome’ characterised by metabolic acidosis, rhabdomyolysis, hepatomegaly and renal failure. Fatal outcomes have been reported (Riker et al. 2009). Midazolam can produce respiratory depression and metabolic acidosis.

Several other agents have been employed in the treatment of RSE. Most have only been investigated in small, open-label, non-randomised and non-blinded clinical studies. Ketamine, an NMDA glutamate receptor agonist and isofluorane have been utilised successfully to treat RSE in children (Kofke et al. 1989; Rosati et al. 2012). While the experience with ketamine in children with RSE is small, its adverse effects appear restricted to hyper-salivation and alterations in liver enzymes.

Although the prognosis of RSE remains generally poor, reasonably good outcomes are occasionally reported after prolonged coma and hospitalisation (Cooper et al. 2009). Long-term prognosis is heavily influenced by predisposing aetiology. A particularly poor prognosis occurs in patients with RSE in the course of encephalitis (Kramer et al. 2005).

**ELECTRICAL STATUS EPILEPTICUS OF SLOW WAVE SLEEP**

**ENCEPHALOPATHY WITH STATUS EPILEPTICUS DURING SLOW SLEEP**

Encephalopathy with status epilepticus during slow sleep (ESES) is an epileptic encephalopathy with heterogeneous clinical manifestations (cognitive, motor, and behavioural disturbances in different associations, and various seizure types) related to a peculiar EEG pattern characterised by paroxysmal activity significantly activated during slow wave sleep that is a condition of continuous spikes and waves, or status epilepticus, during sleep (Fig. 16.22). In the first descriptions, dealing with the most severe cases, diffuse bilateral slow (<2.0Hz) spike–wave complexes occupied 85% or more of the slow sleep time (Jayakar and Seshia 1991; Tassinari et al. 1992; Bureau 1995; Beaumanoir 1995).

However, cases with a spike–wave index of 50–85% are frequent and usually have a similar evolution. We believe that in fact what characterises the syndrome is not the percentage of the characteristic EEG pattern during sleep but the combination of signs of neurocognitive impairment appearing together with a significant increase in EEG abnormalities during sleep. Tassinari, very elegantly labelled ESES as the ‘Penelope syndrome: Spinning during the day, spiking during the night’, in which the diurnal ‘spinning’ to make up a thread.
functions such as learning and memory consolidation during sleep might cause the typical clinical symptoms by suggesting that the abnormal epileptic EEG activity occurring and unilateral focal polymicrogyria, and similar cases have cases. Guerrini et al. (1998c) reported the association of ESES and unilateral focal polymicrogyria, and similar cases have subsequently been observed (e.g. Caraballo et al. 1999). These observations suggest ESES is heterogeneous and caused by multifocal pathological abnormalities. Another organic cause is hydrocephalus, which may be related to thalamic injury (Guzzetta et al. (2005).

The pathophysiological mechanisms underlying this condition are still incompletely understood; recent data suggest that the abnormal epileptic EEG activity occurring during sleep might cause the typical clinical symptoms by interfering with sleep-related physiological functions, and possibly neuroplasticity processes mediating higher cortical functions such as learning and memory consolidation (Tassinari et al. 2009; Bölsterli et al. 2011; Bölsterli Heinze et al. 2014).

Treatment is often disappointing and controlled trials are lacking. Veggiotti et al. (2012) suggested a treatment algorithm based upon a review of the literature (mainly case reports or rather small retrospective studies). Treatment options include some antiepileptic drugs (valproic acid, ethosuximide, levetiracetam, and benzodiazepines), corticosteroids, immunoglobulins, the ketogenic diet, and surgery (multiple subpial transections). Some investigators claim satisfactory results with sulthiame (Gross-Selbeck 1995; Lerman-Sagie 1995; Fejerman et al. 2012). Short cycles of high doses of benzodiazepines (De Negri et al. 1993) are another treatment option. ACTH steroids are, in fact, the most commonly used agents and are considered effective.

In a pooled analysis of 575 published cases, the Utrecht group (van de Munckhof et al. 2015) found that AEDs (n=495) were associated with improvement (i.e. cognition or EEG) in 49% of patients, benzodiazepines (n=171) in 68%, and corticosteroids (n=166) in 81%. Surgery (n=62) resulted in improvement in 90% of patients. In a subgroup analysis of consecutive patients (585 treatments in 282 patients), improvement occurred in a smaller proportion treated with AEDs (34%), benzodiazepines (59%), and corticosteroids (75%), whereas improvement percentage after surgery was preserved (93%). Possible predictors of improved outcome were treatment category, normal development before ESES onset, and the absence of structural abnormalities. Treatment is usually for prolonged periods (months or even years). Recognition of electrical status epilepticus is of great importance as the syndrome is a cause of treatable cognitive deterioration. It is therefore essential to obtain a sleep EEG in such cases, even in the absence of clinical seizures.

LANDAU–KLEFFNER SYNDROME

Landau–Kleffner syndrome (LKS), a condition also called ‘epileptic aphasia’ presents a paroxysmal sleep EEG activity similar to ESES. This syndrome is defined as acquired aphasia that is often but not always predominantly receptive in type in conjunction with intense paroxysmal EEG activity that is more intense in sleep. Awake tracings show uni- or bilateral spike foci often over the temporal lobes (Hirsch et al. 1990; 2006b; Beaumanoir 1992; Maquet et al. 1995). There may be a correlation between the intensity of paroxysmal activity, especially during sleep, and language deterioration. In such cases, there is a rapid or progressive loss of language abilities that often involves mainly verbal auditory discrimination. Approximately 80% of children have seizures that are typically focal but not severe. Atypical absences may occur and are frequently repetitive. In most cases, both the epilepsy and EEG abnormalities disappear before age 15 years (Dulac et al. 1983; Rossi et al. 1999; Hommet et al. 2000).

The outlook for language is poor and most patients continue to experience language difficulties as adults. The severity of the language impairment is variable ranging from almost no verbal ability to mild or moderate deficits in verbal communication (Bishop 1985; Deonna et al. 1989).

Similar EEG activity involving other brain areas may be responsible for disturbance of other functions. Hirsch et al. (1995) reported apraxia associated with continuous parietal EEG paroxysms and suggested a similar mechanism to LKS. Neville and Boyd (1995) suggested that epilepsy may manifest as a gait disorder that responds to corticosteroid treatment.

LKS is highly heterogeneous (Deonna et al. 1977; Hirsch et al. 1990; Maquet et al. 1995; Van Bogaert 2013; Deonna and Roulet-Perez 2016). Some children have predominant disturbances in expressive language or complex patterns of language disturbance. Others do not exhibit the pattern of continuous spike-wave discharges during sleep, and occasionally patients have severe persisting epilepsy.

The mechanism of the syndrome is unclear. PET studies yield heterogeneous results (Maquet et al. 1990; Rintahaka et al. 1995; De Tiège et al. 2004; Luat et al. 2005). Magnetoencephalographic spikes originated in the left auditory area in one study (Paetau et al. 1992), and interictal discharges may be responsible for the aphasia.

Both LKS and ESES are examples of epileptic encephalopathy, illustrating the effects of ‘subclinical’ electrographic
discharges on brain function, and confirming that epilepsy is not limited to seizures and has more pervasive effects. Indeed, some cases of LKS also manifest more diffuse dysfunction, for example, involving the frontal lobes (Roulet et al. 1991; Hirsch et al. 1995). Transient deficits in localised brain functions such as the anterior opercular syndrome (Roulet et al. 1989; Bouloche et al. 1990) have also been linked to intense, localised, paroxysmal EEG activity.

Treatment of the condition is disappointing. Anticonvulsant agents usually fail to abolish the paroxysmal activity or improve language competence, although some success has been reported with the drugs used in ESES (Veggioi et al. 2012; van den Munkhof et al. 2015). Corticosteroids or ACTH treatment is an accepted practice but must be continued for 1 year or more (Lerman et al. 1991). Reports on the efficacy of lamotrigine, sulthiame, felbamate, nicardipine, vigabatrin, levetiracetam, vagal nerve stimulation and the ketogenic diet are limited. Carbamazepine and possibly phenobarbitone and phenytoin occasionally exacerbate the syndrome (Mikati and Shamseddine 2005). Only anecdotal reports are available and the relationship between treatment and language improvement, although generally accepted, remain unproved. The same applies to surgical treatment by multiple temporal transections (Morrell et al. 1989; Devinsky et al. 1994; Morrell et al. 1995; Robinson et al. 2001).

**DIFFERENTIAL DIAGNOSIS FROM PAROXYSMAL DISORDERS OTHER THAN EPILEPSY**

Epilepsy is the most important of the neurological disorders of childhood characterised by paroxysmal manifestations, but a host of other paroxysmal conditions can occur in children. Indeed, the diagnosis of epilepsy is often made incorrectly in the presence of paroxysmal events (Stroink et al. 2003; Xu et al. 2016). An incorrect diagnosis of epilepsy was made in 20–30% of children referred to one epilepsy clinic (Jeavons 1983), in 27 of 124 children (22%) reported by Desai and Talwar (1992), and in 10–20% of children according to Merrick et al. (1991). Such figures reflect a common experience (Aicardi 2003) and remain similar despite recent developments and increased awareness in the field. The misdiagnosis rate of 5% for the diagnosis of epilepsy (Van Donselaar et al. 2006) should be considered an absolute minimum, as the authors acknowledge. A misdiagnosis rate of at least 23% in a British population-based study (Scheepers et al. 2003) may reflect general practitioners and paediatricians without special training in epilepsy playing a central role in diagnosis and treatment. More specialised physicians do better. Neurologists (error rate 5.6%) do better than non-specialists (error rate 18.9%) in another hospital-based UK study (Leach et al. 2005).

Diagnostic inaccuracy is especially common for a first seizure. One-quarter of children were incorrectly diagnosed as having a seizure while the diagnosis of epilepsy was missed in over one-third of children in a study involving 127 children seen in a tertiary care First Seizure Clinic (Hamiwka et al. 2007).

Because an incorrect label of epilepsy all too often has profound consequences on a child’s life, such misdiagnoses must be avoided. So, ideally, all patients suspected of having epilepsy should have an assessment by a child neurologist, but this is not possible in many countries due to available resources (Van Donselaar et al. 2006).

**ANOXIC SEIZURES**

So-called anoxic seizures are due to cortical hypoxic failure of energy metabolism because of anoxia or hypoxia. They may occur in many circumstances: bradycardia of less than 40 beats per minute, tachycardia of more than 150 beats per minute, asystole of more than 4 seconds, systolic pressure less than 50mmHg or venous O2 pressure less than 20mmHg.

Cortical hypoxia results in loss of consciousness and of postural tone. When severe, liberation of tonogenic brainstem centres from corticoreticular inhibition causes decorticate rigidity and/or opisthotonus. Increasing degrees of cortical hypoxia produce slowing of frequency of the dominant cortical rhythms, followed by complete flattening of the EEG tracing, which corresponds to the tonic phase. With correction of hypoxia, slow waves reappear and may be synchronous with a few jerks of the limbs before resumption of normal EEG activity (Gastaut 1974; Stephenson 1990).

Anoxic seizures can be due to several different mechanisms (Table 16.15), several of which may be operative in the same patient or even in the same attack (Stephenson 1990, 2013).

**REFLEX SYNCOPE AND FAINTS**

Syncope refers to a sudden loss of consciousness and postural tone associated with diminished energy substrates to the brain.
Part VII Paroxysmal Disorders

Part VII Paroxysmal Disorders

From primary cardiac events. In faints, the loss of consciousness is generally preceded by sensations of light-headedness. Vasovagal syncopes are often familial in nature (Camfield and Camfield 1990; Cooper et al. 1994) but do not follow Mendelian rules of inheritance.

Possible mechanisms of anoxic seizures

Breath-holding with prolonged expiratory apnoea (Southall et al. 1985) and ventilatory/perfusion mismatch or intrapulmonary shunting (Southall et al. 1990) responsible for cyanosis

Obstructive apnoea especially awake apnoea associated with gastrointestinal reflux (Spitzer et al. 1984)

Vasovagal manoeuvre

Classical and the pulse may slow.

Cardiac disease

Valvular (aortic stenosis)

May be exclusive mechanism in some self-induced syncopes (Gastaut 1980)

Ventricular tachyarrhythmias

Sick sinus syndrome (Gordon 1994b)

Fainting and reflex anoxic seizures

May alternate with ‘true’ breath-holding

Other circulatory syncopes

Vagovagal syncope (Woody and Kiel 1986)

‘Hypervagism’ (Stephenson 1990) Carotid sinus disorders

Brain compression

Chiari malformation (Stephenson 1990)

Brainstem tumours (Southall et al. 1987)

usually through a decrease in cerebral perfusion by oxygenated blood, due to reduction in cerebral blood flow or to a drop of the oxygen content, or to a combination of both. Low perfusion is usually the consequence of a cardio-inhibitory mechanism mediated through the vagus nerve or of a vaso-depressor mechanism with variable vagal accompaniment (vasovagal or neuro-cardiogenic syncope). It may rarely result from primary cardiac events. In faints, the loss of consciousness is generally preceded by sensations of light-headedness, weakness or a feeling of things going far away, and the loss of tone is progressive with the patient slowly slumping to the ground. The loss of posture is occasionally abrupt with a sudden fall. In such cases the tip of the tongue may be cut, though true tongue biting with lateral laceration is unusual (Stephenson 1990; Lempert et al. 1994). Urinary incontinence is not uncommon and does not indicate an epileptic mechanism.

The diagnosis of syncope rests essentially on the circumstances of occurrence which include emotional stimuli or stress, standing posture, especially in a confined atmosphere, or minor pain. In some individuals faints are regularly provoked by the same stimulus such as getting into or out of a bath (Stephenson 1990; Patel et al. 1994), combing one’s hair (Lewis and Frank 1993) or stretching (Pelekanos et al. 1990). Some triggers are so specific as to allow a clinical diagnosis without any investigations; these include venipuncture, ear piercing, and hair grooming, whereas if domestic bathing of an infant is the trigger one may say with confidence that the diagnosis is not syncope (Nechay and Stephenson 2008). During the attack, the patient becomes pale, the eyes may deviate vertically and the pulse may slow.

It is prudent to obtain a12-lead electrocardiogram (ECG) if the history is not typical, but an EEG is not required. One should bear in mind that 2% of typically developing children may have discharges such as rolandic sharp waves and this ‘abnormality’ may lead to diagnostic confusion. Ocular compression during EEG is rarely justified except in exceptional circumstances (Stephenson 2008).

In some cases, a true epileptic attack can be induced by the hypoxia resulting from a syncope (Aicardi et al. 1988; Battaglia et al. 1989; Stephenson 1990). Such instances have been termed anoxic–epileptic seizures (Stephenson 1990; Horrocks et al. 2005) and may be of long duration resulting in episodes of status epilepticus (Battaglia et al. 1989).

Alternatively, cardiac arrhythmias can occasionally result from an epileptic discharge involving cardio regulatory efferents. Such a phenomenon (epileptic–anoxic seizure) may play a role in sudden death of patients with epilepsy (Oppenheimer et al. 1990; Stephenson 1990; Stephenson et al. 2004). The epileptic nature of such episodes may be difficult to diagnose. Home videos are of substantial help for a more accurate diagnosis.

Many synapses have an abrupt onset; clonic movements occur in approximately 50% of cases and incontinence in 10% (Stephenson 1990). Synapses can occur in the sitting and even in the supine position, may be preceded by hallucinatory phenomena or evidence postictal confusion, thus rendering distinction from an epileptic seizure difficult. Vasovagal synapses are mostly a benign phenomenon although they generate considerable anxiety. Reassurance is usually sufficient, but treatment with atropine may be justified for frequent synapses.

Vasovagal synapses are often familial in nature (Camfield and Camfield 1990; Cooper et al. 1994) but do not follow Mendelian rules of inheritance.

Synapses may occur electively in febrile children and such accidents are apt to be mistaken for febrile convulsions. The oculocardiac reflex produces a lasting slowing of the heart rate and may induce a seizure identical to the patient’s usual attack. This mechanism is not universally accepted, as a strong oculocardiac reflex does not exclude the possibility of a febrile convolution.

Niaprazine, an antihistaminic drug is associated with fainting and loss of consciousness. The loss of consciousness is associated with hypotonia and pallor, is of brief duration and occurs within 30 minutes of absorption in most cases (Bodiou and Bavoux 1988). Severe cases are rare (Auduy 1988).
BREATH-HOLDING SPELLS

Breath-holding spells occur in about 4% of all children below the age of 5 years. There are two major forms, the cyanotic and the pallid types (Lombroso and Lerman 1967). The mechanisms of the two forms are different, and most ‘pallid breath-holding attacks’, such as occur when a child bumps her/his head and almost immediately loses consciousness, are best regarded as reflex hypoxic syncopes precipitated by painful stimuli or emotion (Stephenson 1990; Breningstall 1996).

Cyanotic breath-holding episodes are provoked by fright, pain, anger or frustration. The child cries vigorously then holds her/his breath in expiration. This results in cyanosis eventually culminating in loss of consciousness and loss of muscle tone. The latter may be followed by brief body stiffening before respiration resumes and the attack ends. Polygraphic recordings have shown a sequence of slowing of the EEG tracing with bradycardia such as one would expect in the overshoot phase of a Valsalva manoeuvre. Despite their frightening appearance, breath-holding spasms are harmless (Gordon 1987). The mechanism of cyanotic breath-holding spells is still imperfectly known (DiMario and Burleson 1993). Oxygen desaturation and reduction of cerebral blood flow because of increased intrathoracic pressure with decreased venous return play a role. However, cyanosis develops with surprising rapidity and an intrapulmonary right-to-left shunt seems likely as a result of imperfect matching of ventilation to perfusion (Breningstall 1996). Gastaut (1974) distinguished between breath-holding spells and sobbing spasms or sobbing syncopes in which the child would ‘sob intensely and intractably for a long period of time (1–3 minutes) before losing consciousness. Exceptional cases of breath-holding episodes resulting in death have been associated with severe underlying conditions (Southall et al. 1990). Such exceptions do not modify the benign prognosis of the condition.

Pallid breath-holding episodes may exist in isolation or alternate with the cyanotic form in the same child. They accounted for 19% of cases in the study by Lombroso and Lerman (1967). In this type, which is often precipitated by pain, especially from trivial head trauma, the child loses consciousness following a minimum of crying or no crying at all. Pallor is marked and stiffening is the rule. In many such patients, the attack is associated with a period of asystole (cardio-inhibitory syncope) that can also be induced by compression of the eyeballs (Lombroso and Lerman 1967; Stephenson 1980). Urinary incontinence is common. The mechanism is reflex cardio-inhibition resulting in cardiac standstill with a consequent hypoxic attack. The tonic attack on EEG is associated with flattening of the record that follows a run of slow waves. A few clonic jerks are not infrequently observed following the tonic attack (Fig. 16.23).

Pallid breath-holding episodes are more frequently mistaken for epilepsy than the cyanotic forms. The diagnosis rests as much on the fact that all episodes are precipitated by an adequate stimulus as on the seizure description, which
Part VII Paroxysmal Disorders

may be difficult to distinguish by history from an epileptic seizure. Indeed, they may be responsible for anoxic–epileptic seizures (Stephenson 1990; Stephenson et al. 2004; Horrocks et al. 2005). The outlook for this form is also favourable, and explanation and reassurance that the episodes produce no harm and will cease is often followed by a marked diminution of their frequency. Rarely is psychiatric help needed, and no drug treatment is necessary or effective (Gordon 1987). Exceptionally, cardiac pacing has been needed (Wilson et al. 2005).

UNUSUAL TYPES OF REFLEX SYCOPES

Self-induced reflex syecopes are rare but may pose difficult diagnostic problems. Such synecopes are seen in patients with psychosis and cognitive deficiency (Gastaut et al. 1987) and are usually mistaken for absences or drop attacks. Affected children stop breathing and inflate their chest or abdomen, producing a Valsalva manoeuvre. After a few seconds, they turn pale, exhibit a vacant look and a loss of tone that may be limited to the neck or involve the lower limbs with resultant fall. A similar phenomenon is frequently seen in girls with Rett syndrome where it alternates with hyperventilation periods, and rarely occurs in intellectually typical children with behavioural disturbances. The diagnosis rests on a peculiar polygraphic sequence (Gastaut et al. 1987; Aicardi et al. 1988). Video with audio may be sufficient for diagnosis, if attention is paid to the lack of breathing sounds during the ‘breath-hold’. EEG/ECG will document the typical changes if an episode is recorded, with ECG showing a combination of tachycardia and reduction of QRS amplitude by about 50% followed by – after about 10 seconds – rebound bradycardia, and a burst of EEG slow activity.

Management is difficult and no evidence base exists for any particular treatment. Fenfluramine, naltrexone, and the use of a wrestler’s belt have been reported to be effective, at least in the short term (Stephenson 2013).

ANOXIC SEIZURES DUE TO RESPIRATORY OBSTRUCTION

These symptoms are infrequent in children, although accidental suffocation or strangulation may occur. Induction of anoxic seizures by an adult, usually the mother, is a relatively common form of Munchausen by proxy or Meadow syndrome (Rosenberg 2003; Galvin et al. 2005). The diagnosis may be challenging if the mother presses the infant’s face into her breast. The constant presence of the mother at the onset of each episode is an essential clue, with a final diagnosis established by polygraphic recording (Stephenson et al. 2004) or covert EEG–video monitoring, which, however, raises ethical and legal problems (Bauer 2004).

SYCOPES OF CARDIAC ORIGIN

Syncopes of cardiac origin are much rarer than reflex vasovagal or cardio-inhibitory attacks. They represented only 6% of 108 synecopes studied by McHarg et al. (1997). It is important to recognise them as they may be due to dangerous conditions causing sudden death; preventive treatment and monitoring are, therefore, essential.

Cardiac disorders responsible for synecopes include valvular disorders such as aortic stenosis, which can produce synecopes on effort; postoperative conduction blocks; cardiomyopathies sometimes associated with myopathies; and intrinsic disturbances of cardiac rhythm such as Wolf–Parkinson–White syndrome, congenital atrioventricular block and the prolonged Q-T interval syndrome. These syndromes result from channelopathies involving specific sodium or potassium channels and include several distinct syndromes (long and short Q-T syndromes, Brugada syndrome, Ward–Romano syndrome, Jervell–Lange–Nielsen syndrome). Long Q-T syndromes (LQTS) (Crotti et al. 2008) are by far the most common of the cardiac conduction disorders that may present as ‘seizures’.

Molecular genetic studies have shown that at least seven different long Q-T syndromes exist including: potassium channel mutations (LQT2) on chromosome 7q35–q36, sodium channel protein mutation on chromosome 3 (LQT3), ras-1 protein gene mutations on chromosome 11p (Towbin 1995; Sarkozy and Brugada 2005; Wolpert et al. 2005). They are genetically transmitted, which has an impact on diagnosis, counselling and treatment, and may be recessive or dominant (Avanzini et al. 2004). Associated features, for example, deafness in the recessive Jervell–Lange–Nielsen syndrome, may be present. All these syndromes can mimic epilepsy (Gordon 1994; Pacia et al. 1994) and can result in sudden death (Goldenberg et al. 2005).

Occurrence of episodes during sleep or exercise may be a hint to the correct diagnosis. Episodes can also be precipitated by emotion or stress. Such circumstances as well as a family history of sudden death or ‘epilepsy’, or a personal history of chest pains, palpitations or a surgically repaired heart defect require full cardiac investigation. The corrected Q-Tc interval is prolonged in most cases, although occasional cases of cardiac syncope with a normal Q-T have been reported, so the ECG should be systematically recorded with the EEG in patients with unexplained loss of consciousness (Bricker et al. 1984). Prolonged ECG recording and effort test may be indicated in selected cases (Nousiainen et al. 1989), especially when a history of familial syncope or sudden death is present. In some cases, a pacemaker should be inserted as sudden death is possible.

Acute episodes of hyperpnoea and cyanosis are a common feature of congenital cyanotic cardiomyopathies. They may result in loss of consciousness and may be followed by hemiplegia of vascular origin. Severe apnoea may also be a feature of the syndrome of alternating hemiplegia (Bourgeois et al. 1993; Andermann et al. 1995).
EPISODES OF APNOEA OR BRADYCARDIA IN YOUNG INFANTS

NEAR-MISS SUDDEN INFANT DEATH SYNDROME

Study of the sudden infant death syndrome (SIDS) is beyond the scope of this book. However, some near-miss SIDS cases may be easily mistaken for epileptic events, the more so as they can be followed by neurological sequelae and episodes of status epilepticus (Constantinou et al. 1989). Indeed, the true sequence of events may be impossible to establish in some cases. Less severe episodes may manifest as briefer episodes of apnoea, with hypo- or hypertonia and a change of colour that may be wrongly interpreted as epileptic phenomena. Such events may occur in the first few days of life in apparently healthy infants (Grylack and Williams 1996).

The most common cause of seizure-related death in children with epilepsy is sudden unexpected death in epilepsy (SUDEP). SUDEP is relatively uncommon in childhood, but the risk increases if epilepsy persists into adulthood. Although the direct cause of SUDEP remains unknown, death most often follows a generalised convulsive seizure, and the risk of SUDEP is strongly related to drug-resistant epilepsy and frequent generalised tonic–clonic seizures. The most effective SUDEP prevention strategy is to reduce the frequency of seizures (Donner et al. 2017). Screening for infants at risk of sudden death has been investigated extensively. Most studies report no precise correlation between polygraphic recordings and the later occurrence of sudden death (Reerink et al. 1995), so that indications for use of electronic monitors in the home remain unclear. In preterm infants, episodes of marked desaturation can occur without apnoea and remain undetectable by monitoring (Poets et al. 1995). The 2016 updated edition of the Cochrane Review (Maguire et al. 2016) on treatments for the prevention of SUDEP found very low-quality evidence of a preventive effect for nocturnal supervision against SUDEP concluding that further research is required to identify the effectiveness of other current interventions; for example, seizure detection devices, safety pillows, selective serotonin reuptake inhibitors, early surgical evaluation, educational programmes, and opiate and adenosine antagonists in preventing SUDEP in people with epilepsy.

Physicians and other health care professionals have a critical role in supporting families that lose a child to epilepsy. Comprehensive reviews provide health care providers with information needed to discuss the risk of death in children with epilepsy and support families following a loss (Donner et al. 2017; Shankar et al. 2017).

The awake apnoea syndrome consists of apnoeic–bradycardic episodes and may be causally related to the presence of gastro-oesophageal reflux (Pedley 1983; Spitzer et al. 1984; See et al. 1989; Page and Jeffery 2000) or to oesophageal spasm (Fontan et al. 1984). The episodes resemble syncope and are often preceded by restlessness and an apprehensive look and accompanied by opisthotonus, so the misdiagnosis of epilepsy is not rare. Such episodes may respond to the treatment of gastro-oesophageal reflux, although this is debated (Brand et al. 2005).

Other causes of apnoea in neonates and infants appear in Table 16.16.

ALTERNATING HEMIPLEGIA OF CHILDHOOD (AHC)

Alternating hemiplegia of childhood (AHC) was initially described as a variant of hemiplegic migraine. However, the condition is so different from classic migraine that it should be regarded as a specific disorder (Bourgeois et al. 1993). The disease certainly goes undiagnosed in many cases.

The onset of the disorder is almost always in the first year and usually in the first 6 months of life (Panagiotakaki et al. 2010); a few late-onset cases are on record (Mikati et al. 2000). Paroxysmal manifestations appear first, sometimes even in the neonatal period (Aicardi 2002). They consist of episodes of hemiplegia that are never isolated but variously combined with tonic seizures ocular motor manifestations and autonomic phenomena. The clinical findings of 30 ‘historical’ cases, examined by Jean Aicardi and published in the third edition of this book, are listed in Table 16.17. Localised or generalised tonic and dystonic seizures and episodes of nystagmus often precede the hemiplegias by weeks to months.

In an effort to elucidate the natural history of AHC, a European Network for Research on Alternating Hemiplegia collected the data on a large cohort of 157 patients (Panagiotakaki et al. 2010). At inclusion, patients were aged from 9 months to 52 years. The median age at diagnosis was 20 months. All patients experienced hemiplegic episodes; 86.5% reported episodes of bilateral weakness, 88% dystonic episodes, 53% epileptic seizures, 72% developed chorea and/or dystonia and 92% intellectual disability. When data over the course of the illness were examined for the whole cohort, the severity of symptoms did not appear to change, with the exception of abnormal ocular movements and hypotonia that regressed, but did not disappear into adulthood (from 86% to 36% and 76% to 36%, respectively). No statistically significant correlation between a history of severe paroxysmal hemiplegic/dystonic episodes and a worse neurological outcome was identified. Seven patients had died, some of whom experienced severe plegic episodes or epileptic seizures at the time of death. History of severe plegic/dystonic episodes was not found to be an aggravating factor for deceased patients. Based on the above observation the authors concluded that the natural history of AHC is highly variable and unpredictable for individual patients.

The frequency of episodes is usually high, with instances of hemiplegia occurring several times a month and lasting from a few minutes to several days. A characteristic feature in most cases is the occurrence of episodes in which the
### Table 16.16  Main causes of apnoea in infants and children

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<sup>a</sup>Gastrointestinal reflux remains a deleted cause of apnoea.

<sup>b</sup>Exclusion diagnosis.

<sup>c</sup>Apnoea, pallor, cyanosis, impression of imminent death. About half the cases are due to known disorders (respiratory, digestive, neurological or cardiac); the remaining cases are idiopathic and may be related to the sudden infant death syndrome and to sudden unexpected death in epilepsy patients (SUDEP).
hemiplegia shifts from one side to the other, with a period of bilateral paralysis associated with mutism, difficulties in swallowing and drooling (Krägeloh and Aicardi 1980). Severe quadriplegic attacks with amimia, malaise and decreased consciousness are often observed (Fusco and Vigevano 1995). Frightening, possibly life-threatening, episodes of apnoea occur in some patients. A very characteristic feature is the disappearance of all symptoms on falling asleep. In prolonged episodes the child is normal on waking up but all symptoms return within 10–20 minutes. Parents often take advantage of this short period to feed the child.

A benign form has been reported by Andermann et al. (1994). In their two patients, the episodes occurred during sleep. A case associated with paroxysmal dystonia is on record (Kemp et al. 1995).

Nonparoxysmal manifestations are present in all patients after a course of a few months or years and run a progressive course. They include intellectual disability of variable degree, choreoathetosis and dystonia, ataxia and sometimes pyramidal tract signs.

The clinical picture of the classic form is so characteristic that there are few differential diagnoses. Initially, however, the occurrence of unilateral tonic seizures followed by hemiplegia makes the diagnosis of focal epileptic seizures difficult to avoid for physicians not familiar with the disease. In about half the patients, true seizures may occur with or without temporal relationship to the hemiplegias. The differential diagnosis is discussed by Andermann et al. (1995), and the main causes of paroxysmal hemiplegia are listed in Table 16.18.

The cases of cutis marmorata congenita with recurrent alternating hemiplegia described by Baxter et al. (1993) can closely simulate the disorder.

All laboratory investigations and neuroradiological studies including MRI have been negative. Transient muscle mitochondrial abnormalities have been reported (Kemp et al. 1995) but are inconstant (Kyriakides and Drousiotou 1994). SPECT has shown variable changes in perfusion, depending probably on the timing of examination (Andermann et al. 1995). Ictal EEGs show only a moderate slowing on the affected side.

Dominant transmission has been reported in a family with affected members with typical but less severe symptoms and a later onset up to 3 years of age (Mikati et al. 1992), and two pairs of affected monozygotic twins and a few cases of apparently recessive transmission are also on record, but the vast majority of cases are sporadic. Two cases have been attributed to mutation in the second gene of familial hemiplegic migraine, \textit{ATP1A2} (Bassi et al. 2004; Swoboda et al. 2004). However, no mutations in this gene were found by Kors et al. (2004) or in several unpublished cases. Given the difficulty of separating such cases from hemplegic migraine, this attribution remains uncertain.

In 2012, mutations in the \textit{ATP1A3} gene (MIM 182350), located at 19q13.2 [hg19], were identified (Heinzen et al. 2012; Rosewich et al. 2012; Ishii et al. 2013) as the primary cause of AHC (AHC2, MIM 614820).
Table 16.18  Main causes of recurrent hemiplegia in children

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<td>Alternating Hemiplegia od childhood</td>
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AR, autosomal recessive; AD, autosomal dominant; S, sporadic; XR, X-linked recessive.
Mutations in *ATP1A3* are found in approximately 75% of cases and the disease is transmitted as an autosomal dominant trait. The mutations are usually de novo, but some have been found to be transmitted to offspring. The *ATP1A3* gene (23 exons, open reading frame [ORF] contains 3042 base-pairs) encodes the sodium-potassium (Na+/K+) ATPase α 3 subunit (1014 amino acids). Mutations in the *ATP1A3* gene, are also found in patients with dystonia 12 (rapid onset dystonia parkinsonism; RDP MIM 128235) and CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss, MIM 601338) syndrome (Heinzen et al. 2014).

The outcome is variable; some children may reach a normal or borderline intellectual level but most have moderate or severe intellectual disability and almost all have a chronic movement disorder (Aicardi 2002; Panagiotakaki et al. 2012, 2015).

Following the discovery that mutations in the gene *ATP1A3* were prevalent in patients with AHC, clinical data from an international cohort of 155 AHC patients (84 females, 71 males; between 3 months and 52 years), allowed study of the spectrum of different mutations within the *ATP1A3* gene and the correlations with the phenotypes (Panagiotakaki et al. 2015). In total, 34 different *ATP1A3* mutations were detected in 85% (132/155) patients, seven of which were novel. In general, mutations were found to cluster into five different regions.

The most frequent mutations included: p.Asp801Asn (43%; 57/132), p.Glu815Lys (16%; 22/132), and p.Gly947Arg (11%; 15/132). Of these, p.Glu815Lys was associated with a severe phenotype, with more severe intellectual and motor disability. The mutation p.Asp801Asn appeared to confer a milder phenotypic expression, and p.Gly947Arg appeared to correlate with the most favourable prognosis, compared to the other two frequent mutations. Overall, the comparison of the clinical profiles suggested a gradient of severity between the three major mutations with differences in intellectual (*P* = 0.029) and motor (*P* = 0.039) disabilities being statistically significant. For patients with epilepsy, age at onset of seizures was earlier for patients with either p.Glu815Lys or p.Gly947Arg mutation, compared to those with p.Asp801Asn mutation (*P* < 0.001). With regards to the five mutation clusters, some clusters appeared to correlate with certain clinical phenotypes. No statistically significant clinical correlation was found between patients with and without *ATP1A3* mutations (Panagiotakaki et al. 2015).

Treatment with the calcium entry blocker flunarizine (Casaer et al. 1987; Silver and Andermann 1993; Andermann et al. 1995) reduces the frequency and duration of episodes in about half the cases. Other agents, including the NMDA receptor antagonist memantine, which has been found effective in a few patients (Korinthenberg 1996), and chloral hydrate or niaprazine, which if given at the onset of an attack may abort it (Veneselli and Biancheri 1997), are of uncertain efficacy. Treatment with topiramate was reported effective in a few children (Di Rosa et al. 2006; Jiang et al. 2006).

**PAROXYSMAL DISTURBANCES OF CONSCIOUSNESS**

The recurrence of variable degrees of disturbed consciousness from coma and stupor to lethargy and confusion is a common and difficult diagnostic problem. Most of the conditions that give rise to such problems are described in other chapters. Table 16.19 gives a list of responsible disorders to help diagnostic orientation. In most disorders, the diagnosis is suggested by a history of previous similar events and/ or by a family history of similar cases. Metabolic disorders are particularly apt to present with recurrent disturbances of consciousness, often associated with vomiting and precipitated by infections and fasting. The possibility of drug toxicity should always be considered in such cases. A syndrome of idiopathic recurrent stupor (Tinuper et al. 1994; Lugaresi et al. 1998) in adolescents and young adults has been attributed to the accumulation of an endogenous ligand of benzodiazepine receptors, endozepine-4, and may respond to flumazenil, which blocks benzodiazepine receptors. This syndrome has also been reported in children (Soriani et al. 1997). The diagnosis demands exclusion of covert administration of exogenous benzodiazepines (Granot et al. 2004). However, a number of synthetic benzodiazepines are difficult to detect by conventional methods thus casting doubt on the very concept of endozepine stupor (Cortellini et al. 2005). Associated phenomena may include hypothermia in Shapiro syndrome (Sheth et al. 1994) or, rarely, hyperthermia in the so-called reverse Shapiro syndrome (Hirayama et al. 1994).

**ACUTE PSYCHIATRIC MANIFESTATIONS**

Acute psychiatric manifestations represent the second most common cause of epilepsy misdiagnosis. In most cases the resemblance to epileptic seizures is only superficial, and episodes of anxiety, acute phobic episodes, instances of epigastric or laryngeal sensation of pressure, fugues and recurrent episodes of feelings of de-realisation often do not raise major diagnostic problems. However, panic attacks are sometimes mistaken for epilepsy (Genton et al. 1995). Hallucinations due to schizophrenia, or to schizophrenia-like states due to substance abuse, and acute confusional episodes may be difficult to distinguish from some types of nonconvulsive status epilepticus. Recurrent episodes of abnormal paroxysmal behaviour may be due to intermittently manifesting metabolic diseases such as hyperammonaemia or hypoglycaemia, and metabolic screening is indicated when these diagnoses are considered.

**Munchausen syndrome by proxy** may also be regarded as a cause of psychogenic seizures and can cause great diagnostic difficulties. The mothers, most often the offenders, may invent a story of seizures and, sometimes, tell it with great sophistication (Meadow 1984, 1991) or even teach the child that he or
aggression and be associated with reduced consciousness and postictal sleep. However, the episodes may occur following only slight provocations, and aggression is clearly directed, which differs from what is seen in patients with complex partial seizures fighting against restraint.

PSYCHOGENIC NONEPILEPTIC SEIZURES (PSEUDOSEIZURES)

The terms to describe such manifestations have changed over the years. The term ‘pseudoseizures’ is nowadays perceived as pejorative by many patients and has been progressively replaced by psychogenic nonepileptic seizures (PNES). Dickinson and Looper (2012) reviewed the history and terminology of PNES. The majority of published studies of PNES involve studies with small sample sizes and retrospective analysis of data. In a thorough 2007 Cochrane review of PNES non-drug treatment approaches, only three studies were deemed sufficiently rigorous (Brooks et al. 2007).

Some forms of hysterical attacks, psychic or psychogenic seizures, can be very difficult to distinguish from true epileptic seizures (Holmes et al. 1980). They are frequent in adolescents and may occur in children as early as 4 years of age (Kramer et al. 1995). They can occur even during apparent sleep (Harden et al. 2003) and in children with neurodevelopmental impairment (Neill 1990). ‘Pseudoseizures’ are commonly observed in children who also have epileptic seizures and are one important cause of apparent ‘intractability’ of epilepsy. They may also occur in children who have never had epileptic seizures (Holmes et al. 1980; Lesser 1996).

PNES can mimic any type of seizures, especially generalised ones, but unilateral or focal seizures may be seen and even EEG may not be sufficient for differential diagnosis from epileptic seizures as organic frontal seizures may not have an EEG expression. Motor signs can be subtle as trembling, intermittent stiffening or hyperventilation, head shaking, eye fluttering and oromotor activity, or more impressive as generalised violent, thrashing and uncoordinated movements, complex motor activity, and focal motor activity (for a review see Lortie 2013). The unique motor sign clearly associated with PNES is eye closure with active opposition to opening. Chung et al. (2006) reviewed 938 ictal events from 221 patients. They found that ictal eye closure had a sensitivity of 96.2% and a specificity of 98.1% for PNES.

Most PNES differ from true seizures by the nature of movements, which are not typical clonic jerks but rather semi-purposeful activity, by their violent and theatrical expression and by a nonstereotyped pattern. In one series of 21 children (Wyllie et al. 1990), 10 had episodes of unresponsive, generalised limb jerking and thrashing movements, and six had episodes of staring and unresponsiveness. Most children were responsive immediately after the paroxysm.
The average age of 43 patients studied by Lancman et al. (1994b) was 12.4 years at onset of seizures and 15 years when the diagnosis was made. Twenty-one of them received antiepileptic agents, and most episodes consisted of violent uncoordinated movements and generalised trembling, although a few patients had only staring seizures. The average duration of episodes was 5.6 minutes, although Bhatia and Sapra (2005) observed that their patients tended to have long episodes lasting 10–35 minutes. Induction of seizures by suggestion (Lancman et al. 1994a) may be helpful. However, the personality of the parents and/or patient and the way they describe the episodes may give rise to serious difficulties.

Ninety-four of 416 paediatric patients monitored during a 3-year period (23%) were found to have had nonepileptic events (Kurluay et al. 2010). Thirty-eight per cent were diagnosed with psychogenic nonepileptic seizures, of which 72% were adolescents. In children younger than 5 years of age, behavioural events and parasomnias were the most common mimickers of epilepsy. Globally, girls are more often diagnosed with PNES than boys (Irwin et al. 2000; Pakalnis and Paolicchi 2003).

Video alone, including home video, may have a high specificity and sensitivity in selected patients when reviewed by experienced observers (respectively 94% and 93% in a recent study) (Chen et al. 2008). However, the onset of the seizure is generally missed in home videos. Caregivers should also be instructed to capture limb and face movements in order to obtain useful information (Widdess-Walsh et al. 2012). When PNES are suspected they should be investigated with prolonged video-EEG to avoid unnecessary treatment (Lortie 2013).

Some true epileptic seizures, particularly of frontal lobe origin, may suggest hysteria or simulation. Weinstock et al. (2003) reported on five children with ‘hyperkinetic’ episodes mimicking frontal lobe seizures, which are particularly difficult to identify. A nonparoxysmal EEG is an important argument but certainly does not exclude the diagnosis as movement artefacts may render the EEG uninterpretable and normal tracings occur occasionally in ‘organic’ frontal seizures. Close video-EEG observation of the patients and tests of provocation may be necessary to firmly establish the diagnosis (Wyllie et al. 1990). Conversely, recording of typical EEG discharges concomitant to clinical events excludes the diagnosis of PNES.

Pseudo-status epilepticus is relatively frequent in adult patients and can be seen also in children (Tuxhorn and Fischbach 2002). Recognition of such cases is essential as the diagnosis of epilepsy often results in prolonged and increasingly heavier drug therapy, with negative effects.

Pseudoseizures masquerading as absences have been observed in 18 children with hyperventilation syndrome by North et al. (1990). The EEG of these patients showed bursts of slow-wave activity without spikes, corresponding to apparently impaired awareness and responsiveness. A similar EEG change associated with altered responsiveness can be observed during hyperventilation in typically developing children (Epstein et al. 1994).

Once the diagnosis of pseudoseizures is established, drug treatment should be rapidly discontinued. Some form of psychiatric treatment seems beneficial, at least in the short term (Holmes et al. 1980). The short-term outcome was favourable in 16 of the 21 children in the series of Wyllie et al., but only ten of 22 children followed-up for 40 months or more by Lancman et al. (1994b) were seizure-free at last visit. Gudmunsson et al. (2001) found that 14 of 17 children and adolescents with PNES were symptom-free after an average duration of treatment of 1.5 years and could resume school. A firm diagnosis is critical so that a shift away from antiepileptic medication and toward psychiatric therapy becomes possible.

THE HYPERVENTILATION SYNDROME

Hyperventilation syndrome is relatively common, especially in adolescent girls. The term implies that ventilatory effort is greater than necessitated by metabolic demands. Patients complain variably of chest pain, light-headedness and dyspnoea. Pseudo-absence spells and syncopes may suggest the diagnosis of epilepsy. The diagnosis rests on a high index of suspicion and the presence of the typical symptoms. Rebreathing in a plastic or paper bag enables control of the symptoms of an impending attack and has both diagnostic and therapeutic value. Underlying family problems should be looked for, but the outlook is somewhat guarded as many children show chronic anxiety as adults (Herman et al. 1981; Oren et al. 1987).

SEIZURES OF TOXIC ORIGIN

Episodes of sudden loss of consciousness, often with convulsions or other neurological phenomena, should always raise the suspicion of toxicity. Predominantly motor manifestations may occur following use of an increasing number of drugs. Such seizures are often dystonic with recurrent episodes of stiffness, neck hyperextension and opisthotonus. Oculogyric crises are frequent. Any recurrent attack with extrapyramidal manifestation should suggest drug intoxication although this possibility may be denied by the parents or custodians. The drugs most commonly causing symptoms include psychotropic agents such as phenothiazines and butyrophenones (Pranzatelli 1996) and metoclopramide (Leopold 1984), but a vast number of agents produce similar symptoms (Elzinga-Huttenga et al. 2006) and a review of these is beyond the scope of this book. The important point is that any acute neurological or psychiatric manifestation in a child or adolescent should immediately suggest such a possibility and makes a thorough investigation imperative, regardless of the denegations of parents or relatives. A familial susceptibility to drugs may exist. Consciousness is preserved in many cases and this does not rule out intoxication that can produce other neurological manifestations with intact vigilance. Urine examination for the commonly responsible drugs should
be performed, and more specialised research may be required in doubtful cases.

Most acute drug reactions are self-limited. Treatment with intravenous benzotropine or diphenhydramine is useful to control rapidly severe dystonic–dyskinetic attacks, although some cases may be resistant to high doses (Leopold 1984).

**TETANY**

Tetany is a manifestation of peripheral nerve hyperexcitability. The term is often used to designate convulsions due to hypocalcaemia in the newborn infant. In older infants and children, tetany proper is characterised by episodes of tonic muscular spasms and paraesthesias affecting the distal territory of nerves, often precipitated by hyperventilation or limb ischaemia. The clinical manifestations of classic tetany do not appear before 3 months of age. Carpopedal spasm is the most striking manifestation – it appears abruptly and affects the fingers primarily. The spasm is characterised by fingers flexed at the proximal joint and extended at the distal joints, with the thumbs strongly adducted and opposed. The feet may be similarly involved. Consciousness is preserved. Laryngospasm is common and may occur simultaneously with carpopedal spasm or independently. The vocal cords are adducted so that inspiration becomes noisy, and complete interruption of respiration rarely occur.

Between spasms, signs of latent tetany may be present but the Chvostek sign is not characteristic as it occurs in some typically developing children. Nerve hyperexcitability is expressed electrophysiologically by repetitive electromyograph (EMG) activity (multiplets) elicited by cuff-ischaemia of the arm, but is present also in 20–30% of healthy individuals (Eisinger 1987).

Tetany is usually due to hypocalcaemia and/or hypomagnesaemia but may also occur in normocalcaemic states. In such cases, tetany appears to be the consequence of a decrease in the level of ionised calcium with a normal level of total calcium. Decreased ionisation of calcium can be caused by alkalosis from hyperventilation or repeated vomiting as in pyloric stenosis.

Vitamin D deficiency is now a rare cause of tetany. Postoperative hypoparathyroidism and pseudohypo-parathyroidism are more frequently causal (Wilson and Hall 2002). Hypomagnesaemia with secondary hypocalcaemia is more rare (Visudhipan et al. 2005). Calcification of the basal ganglia can be found in patients with hypo-parathyroidism and pseudohypoparathyroidism, headaches and extrapyramidal signs. Additionally, patients with pseudohypoparathyroidism are obese, below average height, with a moon-shaped facies and short metacarpals. Intellectual disability, cataracts, enamel defect and decreased olfaction and auditory acuity are additional features (Ellie et al. 1989). In all types, epileptic seizures can occur at any age and are, in fact, more commonly observed than the muscle spasms of classic tetany.

The treatment of tetany consists of parenteral administration of calcium salts and vitamin D, and occasionally of magnesium salts.

**INVESTIGATIONS IN PATIENTS WITH EPILEPSY**

Epileptic seizures are transient clinical events. Consequently, the identification of an attack as epileptic mainly depends upon reports from the patient and/or other witnesses. History taking is by far the most important ‘investigation’ for the diagnosis of epilepsy; if medical errors, in terms of both diagnosis and treatment choices, are to be avoided. The mainstay of the diagnosis is a good eyewitness account of the episode, but this information may not be available, may be incomplete, misleading or rather vague, and may not correspond to the definition of the various epileptic seizures or syndromes. The results of the additional investigations including EEG may also be uninformative, difficult to interpret, or contradictory.

A detailed description and updates of ancillary investigations are beyond the scope of this section. The reader is referred to the specialised literature on EEG (Daly and Pedley 1990; Blume and Kalbara 1995; Mizrahi et al. 2004; Kaminska et al. 2005; Crespel et al. 2006; Shcomer and Lopes Da Silva 2012), structural and functional neuroimaging (Kuzniecky and Jackson 2005; Gaillard et al. 2009; Chugani 2010; Gaillard et al. 2011; So and Ryvlin 2015; Gaillard and Oluigbo 2016) and neuropathology (Blümcke et al. 2015). Genetic and metabolic screening were treated in the corresponding chapters of this book. Presurgical evaluation strategies, both general and per aetiology can be found in Arzimanoglou et al. (2016).

The first step, following a first paroxysmal event reported by the patient or their family, is to obtain a precise description and formulate a hypothesis about the epileptic or nonepileptic nature of the event. History taking usually requires more than one session because new memories and questions may arise after the first questioning. The family needs to be informed about the importance of focal clinical signs if present, and about other elements that can provide clues to diagnosis and treatment. The parents should be encouraged to record a home video, an invaluable source of information. A detailed description of the clinical paroxysmal events, performed in a rigorous and comprehensive manner, is mandatory.

The accuracy of the diagnosis of epilepsy varies from a misdiagnosis rate of 5% in a prospective childhood epilepsy study in which the diagnosis was made by a panel of three experienced paediatric neurologists (Stroink et al. 2003) to at least 23% in a UK population-based study (Scheepers et al. 2016).
The paediatrician must be familiar with the various types of generalised seizures, their main features and characteristics, and their pattern of appearance. If this is not the case a second opinion should be requested. For example, typical absences usually occur several times a day; infantile epileptic spasms usually occur in clusters; atypical absences are rarely the sole type of seizure in a patient; and tonic seizures are usually encountered in non-idiopathic forms of epilepsy. The difference between generalised tonic–clonic seizures and secondarily generalised seizures must be clearly understood. Before accepting that a seizure is a primarily generalised one, any focal sign preceding the tonic–clonic phase must be carefully sought. A number of practical consequences, in terms of both diagnostic investigations and treatment, will directly result from this first diagnostic step. In case of a doubt initiation of a treatment is not indicated.

The age of the patient at onset of the epilepsy is another essential consideration as several epilepsy syndromes are strongly age-dependent. Consequently, age consideration will provide valuable clues for a precise syndromic diagnosis (see Table 16.9).

A complete neurological and general examination provides other vital diagnostic elements. It should involve especially the skin, the eyes, a search for focal neurological signs and a rapid assessment of the patient's competence both cognitively and socially. The history should include the life history of the patient from birth, early development, past major diseases, educational attainment and socio-professional status.

Although history taking is the cornerstone of diagnosis in epilepsy, and physical examination may give essential clues, technical developments have added considerably to our knowledge in this field and may be of great clinical importance. EEG and neuroimaging are the main investigations performed but functional neuroimaging and biochemical investigations are indicated in selected cases.

The Quality Standards Subcommittee of the American Academy of Neurology recommends routine EEG as part of the diagnostic evaluation; other studies such as laboratory evaluations and neuroimaging studies are recommended as based on specific clinical circumstances (Hirtz et al. 2000). The EEG is important for diagnosis and differential diagnosis (Koutroumanidis et al. 2017a,b) but of little help in the determination of a cause. The child should then be referred to a child neurologist to evaluate the indications for neuroimaging studies and genetic counselling.

**ELECTROENCEPHALOGRAPHY**

An EEG is systematically recorded in children with a first epileptic seizure. However, it is of no value in cases presenting with simple febrile convulsions and in many cases of sporadic seizures. In general, an EEG, like any other investigation, should be required only when some sort of first hypothesis has been formulated. It may identify specific interictal or ictal abnormalities that are associated with an increased epileptogenic potential or a seizure disorder. The request for an EEG should be accompanied by a detailed description of the paroxysmal event and related clinical findings to maximise interpretation of the recording. It is also essential that the recording technique is standardised and that an experienced paediatric electroencephalographer interprets the recording, as the EEG profoundly changes with age, both in terms of background and type of abnormalities. The reader is referred to the specialised EEG literature for details (Daly and Pedley 1990; Blume and Kalbara 1995; Mizrahi et al. 2004; Kaminska et al. 2005; Crespel et al. 2006).

The EEG is indicated as an emergency investigation only in cases of: suspected neonatal seizures, infantile spasms, nonconvulsive status epilepticus, coma of undetermined aetiology, confusional state or neurological signs suggesting a localised brain insult. In all other cases it is preferable to defer the investigation. Following a first unprovoked seizure the quantity of expected information from the standard EEG is generally too low to affect treatment recommendations in most patients (Gilbert and Buncher 2000).

In patients with previously diagnosed epilepsy, systematic repetition of the EEG at each presentation to an emergency department is unwarranted (Arzimanoglou et al. 2004), unless seizure semiology has changed.

EEG information should always be interpreted in conjunction with the clinical history (Koutroumanidis et al. 2017a,b). A normal EEG, even if repeated, does not exclude the diagnosis of epilepsy, nor does an abnormal or even a paroxysmal tracing establish it. The diagnostic yield of the interictal EEG can be increased if the conditions and techniques of recording are based upon a syndromic diagnostic hypothesis (e.g. sleep deprivation EEG when suspecting juvenile myoclonic epilepsy).

**ROUTINE ELECTROENCEPHALOGRAM**

The ‘routine’ EEG of infants and young children should systematically include a sleep record. Standard activation procedures such as hyperventilation and photic stimulation should be included, and eventually adapted to the diagnostic hypothesis (e.g. investigating the spectrum of photosensitivity when suspecting a stimulus-sensitive epilepsy or reaction to low-frequency photic stimulation when suspecting a progressive myoclonic epilepsy).

In occasional cases, the EEG tracings may suggest an aetiology (e.g. the presence of a slow-wave focus may indicate
a focal lesion; localised near-continuous EEG discharges may suggest focal cortical dysplasia). The lateralising and localising value of the EEG has been extensively discussed. Although a consistently focal EEG focus is of considerable value, diffuse paroxysmal EEG abnormalities are not rare in children with focal lesions, especially cortical malformations and developmental tumours (Kahane et al. 2005), and should not contra-indicate the possibility of surgery.

The prognostic significance of the EEG may be clearly established. Slow spike–wave complexes or multifocal spikes with abnormally slow background indicate the likelihood of an unfavourable course. Likewise, an abnormal EEG before discontinuing therapy may be associated with a high recurrence rate (Shinnar et al. 1990, 1994).

In general, however, the EEG is not an essential guide to therapy. The presence of EEG paroxysms is not in itself an indication for drug treatment nor a necessary contra-indication to its discontinuation. In rolandic epilepsy, for example, the EEG may normalise several months or years after cessation of seizures. The greater or lesser amount of paroxysmal EEG activity is rarely, if ever, an indication for stepping up or reducing therapy, except possibly in the case of some epileptic encephalopathies in which there are arguments (but no certainty) for trying to suppress or diminish the EEG epileptic activity. Clinical expertise of the treating physician is essential in interpreting EEG findings.

OTHER ELECTROENCEPHALOGRAM TECHNIQUES

In addition to hyperventilation, intermittent photic stimulation and brief sleep, which are routinely employed, prolonged sleep studies are of great interest under certain circumstances. All-night sleep records are particularly useful in such epilepsy syndromes as the Landau–Kleffner syndrome, and atypical partial benign epilepsy, or when continuous spike–waves of slow sleep are suspected. Sleep EEG is essential for recording nocturnal seizures, for example, in frontal lobe epilepsy. Nap recordings may be sufficient in many cases and should be privileged in children (Peraita-Adrados et al. 2001). Prolonged monitoring is also of value for the surveillance of neonates with seizures and in cases of encephalopathies with EEG-clinical dissociation.

Ambulatory EEG monitoring is a useful technique in cases in which the clinical history and sleep EEG are not sufficient to establish or rule out the diagnosis of epilepsy, and in which seizures are frequent enough to make their occurrence likely during a 24- or 48-hour period. Distinction between true and nonepileptic seizures is one of the best indications for this technique. It also facilitates sleep recording in older children who may not easily fall asleep in the laboratory. However, this technique is much less used nowadays, as ambulatory recording in childhood is prone to artefact and lead disconnection, and lacks video correlation. For these reasons it has been replaced by in-hospital video-EEG monitoring.

Video-EEG recordings (either of short duration conducted in an out-patient monitoring facility or of longer duration during hospitalisation) has become an essential tool for diagnosis and treatment. Its main indication is the recording of ictal phenomena for differential diagnosis, localisation and better syndromic diagnosis. Interictal activity can also be recorded for a longer duration and correlated to behavioural status. Digital EEG acquisition and storage in a format for subsequent re-montaging and filtering have improved the speed and accuracy of ictal recordings and replaced paper recording.

Telemetric EEG monitoring combined with neuropsychological tests has shown that isolated discharges or even single spikes may produce transient cognitive dysfunction (Arts et al. 1988). Their presence does not however require systematic treatment. Indications to treat with AEDs, the choice of the drug to be prescribed and the duration of treatment trial should be evaluated on a case-by-case basis and in collaboration with a paediatric epileptologist (Arzimanoglou et al. 2004).

Video-EEG monitoring of both ictal and interictal activity is essential in the pre-operative evaluation for epilepsy surgery. However, video-EEG monitoring must be interpreted with the assistance of experienced personnel (medical and paramedics) who can test patients during seizures looking for signs and symptoms of localising value such as a transient aphasia, limb dystonia, visual field or memory defects. Other EEG techniques, discussion of which are beyond the scope of this book, include semi-invasive (sphenoidal or ethmoidal electrodes, foramen ovale electrodes) and invasive techniques (extradural, subdural or depth electrode recordings).

NEUROIMAGING IN EPILEPSY

STRUCTURAL NEUROIMAGING

Although abnormalities on neuroimaging are observed in up to one-third of children with a first seizure, most do not influence immediate treatment or management decisions such as the need for hospitalisation or further investigations. Hirtz et al. (2000) reported that imaging results significantly contributed to further clinical management in only 2% of patients. In the majority of these cases imaging had been performed because the seizure was focal or there were specific clinical findings. Thus, there is insufficient evidence to support a recommendation at the level of guidelines for the use of routine neuroimaging, that is, imaging performed for a first non-febrile seizure in a child.

Factors to be considered for non-urgent neuroimaging study include age of the child, need for sedation, EEG results, history of head trauma, and other clinical factors including family history of epilepsy. MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown aetiology, unexplained abnormalities...
on neurological examination, a seizure of focal onset with or without secondary generalisation, or an EEG that is not typical of focal or generalised idiopathic epilepsy, and in children under 1 year of age (King et al. 1998; Hirtz et al. 2000).

Emergency neuroimaging following a first seizure is justified only when the physical and/or neurological examinations suggest a serious condition that may require immediate intervention. Indications include a postictal focal deficit that does not quickly resolve or where consciousness has not returned to baseline within several hours after the seizure. The possible effects of emergency medication used to treat the seizure must be taken into consideration.

In children with an established diagnosis of epilepsy, MRI is clearly preferable to CT (Commission on Neuroimaging 1997). CT may still have special indications, especially for demonstrating calcifications that are better visualised than with MRI. However, neuroimaging is not indicated in idiopathic generalised epilepsy (e.g. childhood absence epilepsy and juvenile myoclonic epilepsy) or a focal seizure associated with an EEG pattern suggesting rolandic epilepsy. Difficulties of interpretation may arise especially when intense convulsive activity is present (Kramer et al. 1987; Yaffe et al. 1995) and excellent quality imaging is mandatory. Special techniques such as 3D acquisition and high-resolution MRI should be used, particularly when investigating focal epilepsies.

There are two major indications for performing MRI:

1. Diagnostic screening in patients with epilepsy associated with an underlying neurological disorder (particularly in cases of epileptic encephalopathy, suspicion of a metabolic or degenerative disorder, etc.);
2. All cases of structural (non-idiopathic) focal epilepsy.

In non-idiopathic focal epilepsies, poor low-field image quality could miss subtle abnormalities despite interpretation by experienced neuroradiologists (Knake and Grant 2006). Consequently, MRI should be performed on a 1.5- or 3T scanner. Several imaging planes are of considerable value for the detection of small lesions such as cortical dysplasias, small indolent tumours and hippocampal sclerosis. Several sequences should be used, including FLAIR, thin cuts, 3D acquisition, reformating in different planes and gadolinium enhancement.

Gaillard and Oluigbo (2016) suggest the following MRI protocol:

**Children 24 months and older**

- High-resolution 3D T1-weighted (SPGR) 1 mm
- Axial and coronal T2
- Axial and coronal flair
- Oblique coronal high-resolution (≤3 m) fast spin echo perpendicular to the long axis of the hippocampus
- Gadolinium not necessary unless tumour or inflammation
- (Magnetisation transfer [better at 1.5T]; DTI, MRS, ASL sometimes used)

**Infants (<2 years) in addition to those 24 months and older**

- Axial, coronal, sagittal (or 3D) T2
- 3D T1 and FLAIR less useful
- If clear abnormality with MRI then proceed to surgical planning (5)
- Source localisation (3D EEG, MEG or fMRI – EEG), FDG-PET, ictal/interictal subtraction SPECT generally equivalent. As a general rule follow institutional availability and expertise – if negative move to next modality (e.g. FDG-PET – if negative then SPECT then MEG). Recognise strengths and limitations of each modality (Jayakar et al. 2014)

The diagnosis of hippocampal sclerosis by MRI rests on unilateral decreased size of the Ammon horn, increased T2 signal and loss of the internal structure of the hippocampal architecture (Jackson et al. 1990; Cendes et al. 1993a, b) (Fig. 16.24). Hippocampal sclerosis is highly correlated with focal seizures of temporal lobe origin (Raymond et al. 1994; Cendes et al. 1995; Cendes 2005). A careful search for additional anomalies is indicated in cases of hippocampal sclerosis, especially with a view to detection of dual pathology (e.g. coexistence of cortical dysplasia).

It is our practice not to recommend neuroimaging studies for children with classic idiopathic generalised epilepsies (absence epilepsy, JME) or for children with typical rolandic epilepsy. Contrariwise, imaging is obligatory for children with all other types of seizures or for any patient with atypical epilepsy. In children with non-idiopathic focal epilepsy that resists AED treatment, we repeat the MRI investigation using high-resolution techniques, preferably after a full revision of the electroclinical presentation of the seizures. Informing the neuroradiologist about the suspected topography of the epileptogenic zone is mandatory.

**FUNCTIONAL NEUROIMAGING AND OTHER TECHNIQUES OF INVESTIGATION**

Functional imaging studies using radiotracers, PET and SPECT, are performed to identify or confirm the ictal focus in the pre-operative evaluation for surgery. The goal of these investigations is to identify eloquent cortical regions and fibre tracts to be spared during epilepsy surgery, and to investigate the pathophysiology of focal and generalised seizure disorders (for detailed reviews see Duncan 1997; Gaillard 2006).

PET allows for the measurement of regional variations in glucose metabolism using $^{18}$FDG (fluoro-deoxyglucose), to map cerebral metabolism by means of $^{15}$O-labelled water; $^{11}$C-flumazenil is utilised to quantify benzodiazepine receptors. The basic aspects and limitations of the technique, the radiopharmaceuticals in epilepsy, the sensitivity of different types of PET investigations, and the practical utility of PET imaging in the presurgical assessment of focal epilepsies has been reviewed (Mauguìere and Ryvlin 2004; Jayakar...
et al. 2014; Gaillard and Oluigbo 2016). Because of its limited temporal resolution, PET does not allow ictal studies but can evaluate interictal glucose metabolism. A correlation has been shown to exist between primary epileptic regions and hypometabolic areas (Chugani et al. 1987; Theodore et al. 1992).

In children with infantile spasms and normal MRI, PET may reveal regional metabolic abnormalities that identify the seizure-onset zone (Chugani et al. 1988). In some children, however, metabolic abnormalities at the onset of infantile spasms resolve with time and thus may represent a functional state that is potentially reversible (Itomi et al. 2002). In children with tuberous sclerosis, the PET tracer $[^{11}\text{C}]$methyl-L-tryptophan (AMT) is claimed to be selectively taken up by epileptogenic tubers (Chugani et al. 1998). If proven, this observation might allow differentiation from non-epileptogenic tubers in the interictal state and facilitate candidate selection (Kagawa et al. 2005). $[^{11}\text{C}]$AMT uptake is also enhanced in focal cortical dysplasia (Fedi et al. 2003; Juhasz et al. 2003). PET studies in Lennox–Gastaut and Landau–Kleffner syndromes reveal mixed results (for a review see Gaillard 2006).

Ictal SPECT compared with an interictal investigation demonstrated regional hyperperfusion in 67–90% of patients (Gaillard 2006) that in a majority of patients correlated with the ictal focus. Such a correlation has been validated with simultaneous intracranial EEG (Spanaki et al. 1999). Seizure localisation using ictal SPECT was also reported in children with intractable epilepsy (Harvey et al. 1993a, b; Cross et al. 1995). False localisation is reported in 3–4% of studies, most probably because of seizure propagation, particularly following late injection times. Subtraction techniques with MRI co-registration improve postictal SPECT localisation of seizure foci (O’Brien et al. 2004). The main technical limitation of this technique derives from the fact that in order for an ictal SPECT study to be useful, the ligand must be injected during the first 10 seconds of seizure onset, which demands a constant surveillance during video-EEG investigations.

Functional magnetic resonance imaging (fMRI) is based on oxygenated haemoglobin giving a different magnetic resonance signal than deoxyhaemoglobin, with increased blood flow to actively discharging neurons resulting in an increased

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**Figure 16.24** MRI scans of both hippocampi of a patient with mesial temporal sclerosis showing details that can be obtained with high-resolution techniques. (Top) Right hippocampus (arrow) is of almost normal size but internal structure cannot be made out. (Bottom) Increased T2 signal in external part of right hippocampus (arrow). (Courtesy Dr G Jackson, Melbourne, Australia.)
signal. The resulting increased oxyhaemoglobin/deoxyhaemoglobin ratio (Morris et al. 1994; Dettre et al. 1995), permits localisation of areas of active brain regardless of whether the activity is normal, for example, voluntary movements, or abnormal, such as epileptic. Functional MRI may have a dual role: (1) to localise epileptic foci by identifying regional blood flow changes that accompany partial seizures; and (2) to map the brain areas such as the motor or language areas that must be respected surgically. Several studies indicate that fMRI language paradigms reliably identify hemispheric dominance for language, including bilateral and right-hemisphere language representation in adults and in children 5 years of age and older (for reviews see Gaillard 2006; Pelletier et al. 2007). This technique is replacing more invasive methods such as intracarotid injection of amytal to determine language localisation (Wada testing) or other essential functions (Pelletier et al. 2007).

Other techniques in clinical practice include magnetoencephalography (MEG), as well as various computerised methods of signal interpretation and EEG topographic studies (e.g. dipole models). MEG registers magnetic brain activity with a high spatio-temporal resolution. It co-registers magnetic spike sources with anatomic MRI, to produce magnetic source imagers to determine the locus of epileptiform activity. Since distortion of magnetic fields by the skin, skull and CSF is negligible, the technique, while still expensive, offers an almost undistorted view of brain activity with a negligible, the technique, while still expensive, offers an almost undistorted view of brain activity with a

The management of epilepsy is not limited to the prescription of drugs. Particularly complicated cases require considerable time, competences, and technical and human resources. In many ‘ordinary’ cases it still requires careful attention, and specialist neurological advice should be sought in most, if not all, cases before starting treatment. The impact of epilepsy on the life of the child and the family group is considerable, and the education and support of parents, counselling and help with educational problems, and management of behavioural difficulties may be even more important than drug therapy of seizures.

**TREATMENT OF EPILEPTIC SEIZURES AND EPILEPSY SYNDROMES**

The management of epilepsy is not limited to the prescription of drugs. Particularly complicated cases require considerable time, competences, and technical and human resources. In many ‘ordinary’ cases it still requires careful attention, and specialist neurological advice should be sought in most, if not all, cases before starting treatment. The impact of epilepsy on the life of the child and the family group is considerable, and the education and support of parents, counselling and help with educational problems, and management of behavioural difficulties may be even more important than drug therapy of seizures.

**EDUCATION OF PARENTS AND CHILDREN**

Because the impact of the diagnosis of epilepsy is not only – or not even essentially – concerned with the rational aspects but has also to take into account misconceptions and prejudices traditionally associated with seizure disorders, a personalised, yet full, explanation should be given to the patient and family. The misconception that epilepsy is a disease ‘in its own right’ should be dispelled, and the concept of epileptic seizures as symptoms of brain dysfunction should be discussed thoroughly. Preconceived entrenched ideas, for example, that all epilepsies are life-long or related to psychiatric disorders, should be discussed and dispelled, as should the frequently expressed fear that brain tumours or other serious brain disorders are a common cause (Brett 1997; Arzimanoglou et al. 2004). A full set of information cannot be given in one session, and repeated interviews are required. Families need time to build and verbalise their concerns. Similarly, the treating physician often needs time to establish a definite diagnosis of the type of epilepsy and its underlying aetiology, a prerequisite for an optimal response to treatment and accurate prognosis.

A full explanation of the aims of therapy, its shortcomings and potential risks of discontinuation. This is essential for the establishment of a confident relationship between patient and physician (Aicardi and Taylor 1998).

It is extremely important to provide a clear understanding of permitted activities and what restrictions are warranted. Restrictions should be limited to a reasonable minimum, with the knowledge that some risks are unavoidable. Swimming is possible with adequate one-to-one supervision.
The use of a bicycle (except on safe roads), and especially of a motorbike, is one of the most difficult problems and can be solved only individually and often imperfectly. Sports such as tennis, football or basketball or gymnastics should be encouraged. Scuba diving and water cave diving should not be permitted.

**DRUG TREATMENT**

**GENERAL PRINCIPLES**

Drug treatment is the therapy of choice for the vast majority of children with seizure disorders. The main drugs currently available are shown in Table 16.20 and primary pharmacokinetic data is given in Table 16.21.

A number of wide-spectrum AEDs have been developed during the last 25 years, including lamotrigine, levetiracetam, topiramate, felbamate, zonisamide and rufinamide. Perampanel is also a promising wide spectrum agent. Others, such as oxcarbazepine, eslicarbazepine, gabapentin, vigabatrin and pregabaline are excellent alternatives for the control of focal seizures. Controlled data in young children are usually lacking, and the drugs are often used out of licence. Data from clinical trials in adults, extrapolated to predict benefits in paediatric patients, often result in fewer or smaller trials being required to obtain a new drug license for children (Wadsworth et al. 2016; Pellock et al. 2017a).

A systematic review of 30 adjunctive therapy focal onset seizures trials supported the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with focal seizures (Pellock et al. 2012). Effect measures were consistent between adults and children for gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate. Placebo-subtracted median per cent seizure reduction between baseline and treatment periods (ranging from 7.0% to 58.6% in adults and from 10.5% to 31.2% in children) was significant for 40 out of 46 and six out of six of the treatment groups studied. The ≥50% responder rates (2.0–43.0% in adults and 3.0–26.0% in children) was significant for 37 out of 43 and five out of eight treatment groups (Pellock et al. 2012).

Unconventional agents such as ACTH and corticosteroids are extremely potent drugs for the treatment not only of infantile spasms but also of other types of resistant epilepsy, especially when cognitive and/or major behavioural disturbances appear. They deserve a full trial (2–4 weeks or more) in such cases.

The mode of action of AEDs is beyond the scope of this book (for reviews see Levy et al. 2002; Wyllie et al. 2006, 2011; Pellock et al. 2017b) and still imperfectly known. Steps from absorption through entry and distribution into the brain constitute the pharmacokinetics of a drug. Considerable knowledge has accumulated over the past two decades about the pharmacokinetics of AEDs, especially in children (Dodson and Pellock 1993; Kearns et al. 2003; Booth and Evans 2004). Later steps with resulting changes in neuronal excitability constitute the pharmacodynamic phase of drug action. Initial pharmacokinetic steps (from absorption to brain entry) are reflected in the blood levels of a drug (Landmark et al. 2016). It has been shown that the blood levels of AEDs are more closely related to brain levels than to the dosage ingested, which is the rationale for their determination. However, blood levels are only one link in the chain of processes that take place between ingestion of a drug and its therapeutic and other effects, and their relationship to brain levels and to levels at the receptors are not necessarily close. Such discrepancies are frequent with sodium valproate and can also occur with carbamazepine (Suzuki et al. 1991, 1994).

**INSTIGATION OF TREATMENT**

Initiating antiepileptic drug treatment is an important clinical decision that requires a firm diagnosis of epilepsy. Consequently, drug therapy should not be initiated for children with paroxysmal events of uncertain origin (Arzimanoglou et al. 2004), or in patients with a single seizure (unless it is of a type allowing a firm diagnosis of an epilepsy syndrome) or for those with epileptic EEG abnormalities without clear-cut clinical manifestations or consequences (Hirtz et al. 2000; Arts et al. 2004; Beghi 2007). Likewise, preventive drug treatment for patients with potentially epileptogenic brain lesions is of unproven value and best avoided as it may result in years of useless drug therapy (Shinnar and Berg 1996).

The problem posed by children with interictal EEG discharges and non-seizure behaviours or cognitive decline is challenging. EEG paroxysms may play a role in some cases (Nicolai et al. 2006), especially if prolonged. Treatment is clearly indicated for some syndromes of severe cognitive decline such as ESes or the LKS (see Encephalopathy with Status Epilepticus During Slow Sleep (ESes) and Landau–Kleffner Syndrome sections), even though there is only anecdotal evidence of efficacy. As these syndromes are typically treatment-resistant, assessing their responsiveness to therapy may prove difficult. Most clinicians are disinclined to treat children with learning difficulties or attention deficit based solely on interictal EEG anomalies. Treatment decisions should, therefore, be evaluated on an individual basis by an experienced child neurologist with competences in both epilepsy and neurophysiology.

Children with two or more seizures or those with a first seizure predictive of chronic epilepsy are candidates for drug treatment. Treatment for patients with infrequent seizures, seizures that are clinically restricted or that occur at socially ‘convenient’ times may not require immediate therapy. The decision to initiate treatment also depends heavily on lifestyle preferences if seizures are relatively rare (Beghi 2007). The decision has to be taken in concertation with the family by a child neurologist specialised in epilepsy.
<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Indication</th>
<th>Total daily dose*</th>
<th>Number of daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Epileptic spasms; West syndrome; Lennox–Gastaut syndrome; Dravet syndrome; ESES;</td>
<td>0.1–10IU/kg</td>
<td></td>
</tr>
<tr>
<td>Carbamazepineb</td>
<td>Focal seizures, generalised tonic–clonic seizures</td>
<td>10–20mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Clobazam</td>
<td>All forms, including Landau–Kleffner syndrome and ESES</td>
<td>0.25–1.0mg/kg</td>
<td>2–3</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Prolonged seizures; Status; tonic–clonic seizures; drug resistant focal seizures</td>
<td>0.05–0.2mg/kg</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Epileptic spasms; West syndrome; Lennox–Gastaut syndrome; Landau–Kleffner syndrome and ESES</td>
<td>2mg/kg (prednisolone); 10–15mg/kg (hydrocortisone)</td>
<td></td>
</tr>
<tr>
<td>Diazepamg</td>
<td>All forms, mainly status epilepticus and febrile convulsions</td>
<td>0.25–1.5mg/kg; i.v. 0.1–0.3mg/kg; rectally 0.5–1mg/kg</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Absences and myoclonic seizures; ESES;</td>
<td>20–40mg/kg</td>
<td>1–2</td>
</tr>
<tr>
<td>Felbamatef</td>
<td>Lennox–Gastaut syndrome; refractory focal seizures</td>
<td>Up to 45mg/kg</td>
<td>2–3</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Focal and secondarily generalised seizures</td>
<td>20–50mg/kg</td>
<td>2–3</td>
</tr>
<tr>
<td>Lamotriginee</td>
<td>Focal and secondarily generalised seizures; tonic–clonic (generalised) seizures; absence seizures; myoclonic seizures (see also text); Lennox–Gastaut</td>
<td>Also on enzyme inducer: 5–15mg/kg/day; Also on sodium valproate: 1–5mg/kg/day</td>
<td>2 (or 1)</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Focal and secondarily generalised seizures</td>
<td>4–12mg/kg/day</td>
<td>2</td>
</tr>
<tr>
<td>Levetiracetamc</td>
<td>Focal and secondarily generalised seizures; tonic–clonic (generalised) seizures; myoclonic seizures</td>
<td>40–60mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Lorazepamg</td>
<td>Status epilepticus</td>
<td>0.05mg/kg i.m. or i.v.</td>
<td>Occasional</td>
</tr>
<tr>
<td>Midazolamg</td>
<td>Prolonged or serial tonic–clonic seizures; status epileptican</td>
<td>Buccal; 0.1–0.2mg/kg intramuscular</td>
<td>Occasional</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>Infantile spasms, myoclonic epilepsies</td>
<td>0.25–1.0mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Focal and secondarily generalised seizures; tonic–clonic (generalised) seizures</td>
<td>4–12mg/day</td>
<td>1</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Generalised convulsive seizures, focal seizures</td>
<td>3–5mg/kg &lt;5 years; 2–3mg/kg &gt;5 years</td>
<td>2 (or 1)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Generalised convulsive seizures, focal seizures</td>
<td>8–10mg/kg &lt;3 years; 4–7mg/kg &gt;3 years</td>
<td>2</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Drop attacks; Lennox–Gastaut syndrome; drug resistant focal seizures</td>
<td>Up to 45mg/kg/day</td>
<td>2</td>
</tr>
<tr>
<td>Sodium valproate,</td>
<td>Generalised tonic–clonic and focal seizures; myoclonic seizures; absences; idiopathic generalised epilepsies</td>
<td>20–50mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>valproic acidb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiripentol</td>
<td>Dravet syndrome; drug resistant focal seizures</td>
<td>50–100mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Focal and secondarily generalised seizures; myoclonic seizures; Lennox–Gastaut syndrome; Dravet syndrome;</td>
<td>1–5mg/kgf</td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Infantile spasms, refractory focal seizures</td>
<td>40–100mg/kg (up to 150mg/kg for infantile epileptic spasms)</td>
<td>2</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Focal and generalised seizures; epileptic spasms</td>
<td>5–15mg/kg</td>
<td>2</td>
</tr>
</tbody>
</table>

Lack of controlled studies for the use of AEDs in children often obliges the use of off-licence drugs. This table does not take into account local legal authorisations for the use of AEDs.

*Oral administration unless otherwise noted (i.v. = intravenously, i.m. = intramuscularly).

Slow release preparation available.

May aggravate myoclonic and absence seizures.

Progressive increase in dose especially important.

Oral, liquid and i.v. preparations available.

For refractory cases only.

For acute treatment of status.

ACTH, adrenocorticotropic hormone; ESES, electrical status epilepticus in sleep.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral availability (%)</th>
<th>T max (hour)</th>
<th>% protein bound</th>
<th>Apparent volume of distribution (L/kg)</th>
<th>Elimination half-life (hour)</th>
<th>Route of elimination</th>
<th>Therapeutic range (mg/L) (mmol/L)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>70–80</td>
<td>2–10</td>
<td>60–80</td>
<td>0.8–1.6</td>
<td>8–24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4–12</td>
<td>17–50</td>
<td>Auto-induction common; induction of other drug metabolism; multiple interactions</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>90</td>
<td>1–3</td>
<td>90</td>
<td>0.7–1.6</td>
<td>10–30</td>
<td>Not established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>75</td>
<td>1–2</td>
<td>95</td>
<td>1.1–1.8</td>
<td>10–20</td>
<td>40% excreted unchanged</td>
<td>15–0.25</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>90–100</td>
<td>1–4</td>
<td>0</td>
<td>0.6–0.9</td>
<td>20–40</td>
<td>Hepatic metabolism</td>
<td>40–100</td>
<td>Not an enzyme inducer</td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>100%</td>
<td>1–4H&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤40%</td>
<td>–</td>
<td>13–20H</td>
<td>Renal</td>
<td>Not established</td>
<td>ESL has a stronger affinity for voltage-gated sodium channels than CBZ or OXC; ESL decreases the levels of steroid contraceptives</td>
</tr>
<tr>
<td>Felbamate</td>
<td>&gt;90</td>
<td>2–6</td>
<td>22–25</td>
<td>0.7–0.8</td>
<td>2–6</td>
<td>90% renal</td>
<td>Not established</td>
<td>Inhibits elimination of valproate, carbamazepine epoxide, phenytoin and phenobarbitone</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>51–72</td>
<td>2–3</td>
<td>0</td>
<td>0.57</td>
<td>5–7</td>
<td>&gt;90% renal</td>
<td>Not established</td>
<td>No drug interaction</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>98</td>
<td>2–3</td>
<td>55</td>
<td>0.9–1.3</td>
<td>12</td>
<td>5% hepatic in enzyme-induced patients, 25% in patients on sodium valproate</td>
<td>Not established</td>
<td>No drug interaction</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>100%</td>
<td>1–6H&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15%</td>
<td>0.6</td>
<td>13 H</td>
<td>Route of elimination for Lacosamide above</td>
<td>Not established</td>
<td>Plasma concentrations not affected by food intake or co-medications</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>&gt;95%</td>
<td>1.3</td>
<td>0</td>
<td>0.5–0.7</td>
<td>5–7</td>
<td>Renal</td>
<td>Not established</td>
<td>No drug interaction</td>
</tr>
<tr>
<td>Drug</td>
<td>Oral availability (%)</td>
<td>(T_{\text{max}}) (hour)</td>
<td>% protein bound</td>
<td>Apparent volume of distribution (L/kg)</td>
<td>Elimination half-life (hour)</td>
<td>Route of elimination</td>
<td>Therapeutic range (mg/L) (mmol/L)</td>
<td>Remarks</td>
</tr>
<tr>
<td>-------------------</td>
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<td>-----------------------------</td>
<td>------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------</td>
<td>----------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Perampanel</td>
<td>100%</td>
<td>0.5–1H (fasten), 3H (fed)</td>
<td>95%</td>
<td>1.1</td>
<td>105</td>
<td>Hepatic metabolism</td>
<td>Not established</td>
<td>Inducing drugs increase perampanel clearance, thus reducing exposures</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>80–100</td>
<td>2–10</td>
<td>50</td>
<td>0.51–0.57</td>
<td>37–7(\text{a})</td>
<td>Hepatic metabolism</td>
<td>10–30 (45–130)</td>
<td>Enzyme inducer</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>80–95</td>
<td>4–12</td>
<td>90</td>
<td>0.5–0.7</td>
<td>9–40</td>
<td>Saturable hepatic metabolism</td>
<td>10–20 (40–80)</td>
<td>Zero order kinetics makes small change of dosage result in wide changes of level; numerous interactions</td>
</tr>
<tr>
<td>Primidone</td>
<td>90–100</td>
<td>0.5–4</td>
<td>10–20</td>
<td>0.4–0.8</td>
<td>5–10</td>
<td>Hepatic metabolism, active metabolites (PEMA(e^+) + phenobarbitone) 40% excreted unchanged</td>
<td>5–12 (25–50)</td>
<td>Metabolised to PEMA(e^+) and phenobarbitone</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>85%</td>
<td>4–6H</td>
<td>35%</td>
<td>50–80</td>
<td>6–10</td>
<td>Renal</td>
<td>Not established</td>
<td>Absorption improved with food; valproic acid decreases the clearance of rufinamide</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>100</td>
<td>1–3</td>
<td>90</td>
<td>0.10–0.20</td>
<td>7–15</td>
<td>Hepatic metabolism, active metabolites (PEMA(e^+) + phenobarbitone) 40% excreted unchanged</td>
<td>50–100 (345–690)</td>
<td>Not an enzyme inducer; mildly inhibits oxidative metabolism; full pharmacological action may require weeks</td>
</tr>
<tr>
<td>Topiramate</td>
<td>80</td>
<td>2</td>
<td>13–17</td>
<td>Not known</td>
<td>21</td>
<td>70% renal, 30% metabolised</td>
<td>Not established</td>
<td>Phenytoin, carbamazepine decrease levels by 40%, sodium valproate by 14%</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>60–80</td>
<td>1–4</td>
<td>0</td>
<td>0.6–0.10</td>
<td>5–7(\text{a})</td>
<td>Excreted largely unchanged</td>
<td>Not established</td>
<td>No drug interaction</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100%</td>
<td>–</td>
<td>50%</td>
<td>1.0–1.9</td>
<td>60</td>
<td>Hepatic metabolism</td>
<td>Not established</td>
<td>Clearance of ZNS in children less than 4 years old is faster than occurs in older children and adolescents by a factor of 1.7</td>
</tr>
</tbody>
</table>

\(\text{a}\)\(T_{\text{max}}\) = time to peak plasma level after administration of single dose.

b\(T_{\text{max}}\) may exceed 100 hours in the first 2 weeks of life.

\(\text{c}\)\(T_{\text{max}}\) in patients receiving the dose chronically, when auto-induction has developed, or receiving other inducing agents.

\(\text{d}\)\(T_{\text{max}}\) in patients receiving the drug as monotherapy, before development of induction.

\(\text{e}\)PEMA = phenylethylmalonamide.

\(\text{f}\)Not significant as the drug binds irreversibly to glutamate-transaminase thus increasing brain GABA level, therefore the important half-life is that of restoration of enzyme level.
CHOICE OF DRUG(S)

The choice of drug(s) depends preferably on the epilepsy syndrome or, if this not yet identified, on the type of seizure(s) experienced by the patient (Arzimanoglou 2002; Whelless et al. 2007; Wilmshurst et al. 2015a, b; Pellock et al. 2017b). Table 16.22 indicates an order of preference for the usual AEDs in the most frequent types of childhood epilepsy.

Any choice is of necessity arbitrary, in part because neither efficacy nor adverse drug effects are fully predictable (Arzimanoglou et al. 2004). Selection of the first drug is often dependent on toxicity, adverse effects and ease of administration as the effectiveness of several different drugs is often comparable. This does not apply to absence seizures and many myoclonic seizures for which mostly sodium valproate, ethosuximide, levetiracetam and the benzodiazepines are indicated. Comparative studies both in adults (Mattson et al. 1992; Richens et al. 1994) and in children (Verity et al. 1995; de Silva et al. 1996) have failed to show significant differences in the efficacy of conventional drugs (phenobarbitone, phenytoin, carbamazepine, sodium valproate) used as monotherapy for focal or generalised convulsive seizures. These results do not exclude the possibility of some agents being more effective in subsets of patients or individual cases.

Some agents are more efficacious in generalised epilepsy or control both focal and generalised seizures (sodium valproate, lamotrigine, levetiracetam, topiramate, zonisamide) while others are indicated for focal seizures only (carbamazepine, gabapentin, oxcarbazepine, vigabatrin). Some agents may aggravate rather than improve certain forms of epilepsy (e.g. carbamazepine for genetic [idiopathic] generalised epilepsies or syndromes with predominantly myoclonic seizures or typical absences; lamotrigine in some cases of young children with Dravet syndrome). However, while this applies for the initial choice of drugs, in resistant cases with tonic–clonic seizures applying too strict rules may be counterproductive.

In many instances the likelihood of adverse effects is critical for drug selection. Major adverse effects are rare (see Adverse Effects of Antiepileptic Drugs section), but even relatively mild effects may significantly impact quality of life. Thus, given the choice between carbamazepine, phenobarbitone and phenytoin, carbamazepine is often preferred in childhood epilepsy due to its ease of administration and lack of effect on cognition (phenobarbitone), or gingival hyperplasia and hirsutism (phenytoin). New generation AEDs have better short- and long-term tolerability than older antiepileptic agents and are preferred as a first choice.

MONOTHERAPY VERSUS POLYTHERAPY

Single drug administration is associated with fewer and less confusing side effects than multiple agents and diminishes drug interactions. Therefore, treatment should almost always be started with a single agent. Seventy to 90% of newly diagnosed, common forms of epilepsy are controlled with monotherapy (Forsythe and Sills 1984; Brodie 1990; Kwan and Brodie 2000a, b, 2001).

Drug combinations should be considered after single drugs in correct dosages have failed to control seizures for a substantial period. However, sequential monotherapy should precede the use of multiple therapy as the value of adding a second drug is often uncertain. Approximately 10–15% of patients so treated have improved seizure control, but a few patients may deteriorate and there is a likelihood of increasing side effects.

Combinations of more than two drugs are rarely indicated (Aicardi and Shorvon 1998; Arzimanoglou et al. 2004). No consensus exists on the number of monotherapy trials that should be attempted before combination therapy is introduced, but at least two appropriate AEDs at the maximally tolerated dose should be tried. Evidence from open clinical trials in adolescents and adults (Kwan and Brodie 2000b, 2001) has shown that full control of seizures is only rarely obtained from a third drug when the first two have failed. This probably applies to children as well. However, the occurrence of two types of seizures in the same patient (e.g. LGS or Dravet syndrome) that require different therapy (Aird et al. 1984; Perucca and Levy 2002) sometimes justifies the early introduction of combination therapy. Even in such cases, however, the use of some modern drugs with a large spectrum of action (e.g. valproate, lamotrigine, levetiracetam, topiramate) may obviate the need for polytherapy.

MODE OF ADMINISTRATION

In principle, the use of more than two doses per day is to be avoided except in cases of very resistant epilepsy treated with drugs of short half-life. Some drugs, for example, phenobarbitone, vigabatrin or lamotrigine, may be given in a single evening dose in older children and adolescents. Sodium valproate can also be used as a single dose in adolescents (Covanis and Jevons 1980).

Gradually increasing or decreasing drug dosage on drug initiation or withdrawal is essential. The first or successive drug should be introduced at low dosage and titrated gradually until control is obtained or the limit of tolerance reached. This is especially important with lamotrigine as the frequency of allergic hypersensitivity rashes increases with rapid introduction. Slow withdrawal is also important for barbiturates, vigabatrin and felbamate, whose rapid discontinuation may induce status epilepticus. However, in the common epilepsies of childhood, withdrawal over 4–8 weeks did not seem to be associated with a higher recurrence rate (Dooley et al. 1996).

When a first drug has failed and another is introduced, the first agent should be withdrawn progressively. It should be remembered that achievement of a stable drug level requires approximately four plasma half-lives. The time to achieve stable levels may be much longer as the dose is usually gradually increased and as phenomena of induction progressively modifies (usually shortens) the apparent drug half-life.
### Table 16.22 Epilepsy syndromes and choice of antiepileptic drugs (AEDs)*

<table>
<thead>
<tr>
<th><strong>Idiopathic (Genetic) generalised epilepsies</strong></th>
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<tbody>
<tr>
<td><strong>Childhood absence epilepsy</strong></td>
<td></td>
</tr>
<tr>
<td>First choice: sodium valproate, ethosuximide</td>
<td></td>
</tr>
<tr>
<td>Second choice: association with lamotrigine</td>
<td></td>
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<tr>
<td><strong>Juvenile absence epilepsy</strong></td>
<td></td>
</tr>
<tr>
<td>First choice: sodium valproate, lamotrigine</td>
<td></td>
</tr>
<tr>
<td>Second choice: association with lamotrigine or topiramate or levetiracetam</td>
<td></td>
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<tr>
<td><strong>Juvenile myoclonic epilepsy</strong></td>
<td></td>
</tr>
<tr>
<td>First choice: sodium valproate, levetiracetam</td>
<td></td>
</tr>
<tr>
<td>Second choice: association with lamotrigine or topiramate or levetiracetam</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Avoid treatment with oxcarbazepine or carbamazepine</td>
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<thead>
<tr>
<th><strong>Idiopathic focal epilepsies (self-limited)</strong></th>
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<tbody>
<tr>
<td>First choice: abstinence if possible (depending on age, frequency and duration of seizures)</td>
<td></td>
</tr>
<tr>
<td>Second choice: sodium valproate or gabapentin or sulthiame</td>
<td></td>
</tr>
<tr>
<td>Third choice: benzodiazepines, preferably clobazam</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Aggravation has been reported in cases of rolandic epilepsy and related syndromes (Landau–Kleffner; CSWSS) when using carbamazepine or oxcarbazepine. However, this is not a constant feature and these drugs are frequently used, particularly in occipital idiopathic epilepsies (Panayiotopoulos and Gastaut type)</td>
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<thead>
<tr>
<th><strong>Structural focal epilepsies</strong></th>
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<tbody>
<tr>
<td>First choice: lamotrigine, sodium valproate, oxcarbazepine, carbamazepine, levetiracetam, gabapentin</td>
<td></td>
</tr>
<tr>
<td>Second choice: lacosamide, perampanel topiramate</td>
<td></td>
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<tr>
<td>Third choice: association of two AEDs</td>
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</tr>
<tr>
<td><strong>Remark:</strong> All AEDs, with the exception of ethosuximide, are indicated for the treatment of focal seizures.Choice depends on tolerance, experience of the treating physician cost and local legal authorisation issues.Failure to fully control seizures with more than two AED trials indicates that the child should be evaluated by a specialised paediatric epilepsy team</td>
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<tr>
<th><strong>Epileptic encephalopathies</strong></th>
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<tr>
<td><strong>Infantile spasms and West syndrome</strong></td>
<td></td>
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<tr>
<td>First choice: vigabatrin</td>
<td></td>
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<tr>
<td>Second choice: ACTH or hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>Third choice: benzodiazepines (nitrazepam), sodium valproate</td>
<td></td>
</tr>
<tr>
<td><strong>Dravet syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>First choice: sodium valproate</td>
<td></td>
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<tr>
<td>Second choice: association of sodium valproate, clobazam and stiripentol</td>
<td></td>
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<tr>
<td>Third choice: topiramate usually in association with one or two of the above</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Avoid treatment with lamotrigine, phenobarbital or carbamazepine, particularly at the early stages of the disorder</td>
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<tr>
<th><strong>Epilepsies with myoclonic–astatic seizures (Doose and related syndromes)</strong></th>
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<tbody>
<tr>
<td>First choice: sodium valproate</td>
<td></td>
</tr>
<tr>
<td>Second choice: association of sodium valproate and lamotrigine, particularly if tonic–clonic seizures or drop-attacks predominate, or association of sodium valproate and levetiracetam or ethosuximide when myoclonic or astatic seizures predominate</td>
<td></td>
</tr>
<tr>
<td>Third choice: topiramate</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Avoid treatment with oxcarbazepine or carbamazepine</td>
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<table>
<thead>
<tr>
<th><strong>Lennox–Gastaut syndrome</strong></th>
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<tbody>
<tr>
<td>First choice: sodium valproate</td>
<td></td>
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<tr>
<td>Second choice: association of sodium valproate and lamotrigine</td>
<td></td>
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<tr>
<td>Third choice: association of clobazam; or topiramate or rufinamide; association of felbamate</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Avoid the association of more than three AEDs; steroids may be useful to tide-up during periods of aggravation</td>
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</table>

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<tr>
<th><strong>Syndrome of continuous spike–wave during slow sleep (CSWSS) and related disorders</strong></th>
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</thead>
<tbody>
<tr>
<td>First choice: benzodiazepines, particularly clobazam, or sulthiame</td>
<td></td>
</tr>
<tr>
<td>Second choice: prednisone or hydrocortisone (steroids can also be considered as a first choice)</td>
<td></td>
</tr>
<tr>
<td>Third choice: association of benzodiazepines and ethosuximide or levetiracetam or sodium valproate or sulthiame</td>
<td></td>
</tr>
<tr>
<td><strong>Remark:</strong> Avoid carbamazepine and oxcarbazepine</td>
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</tr>
</tbody>
</table>

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*Lack of controlled studies for the use of AEDs in children often obliges the use of off-licence drugs. This table does not take into account local legal authorisations for the use of AEDs.*
The treating physician must be convinced that in everyday clinical practice a rapid titration of an AED is only exceptionally indicated. The families also need to be informed about the expected delays in achieving stable, and hopefully efficacious, drug levels. Two of the most frequently observed medical errors include overly rapid substitution of a newly prescribed AED or too early instigation of adjunctive treatment.

**MONITORING OF ANTISEIZURE DRUG THERAPY**

Regular clinical supervision of children on antiepileptic drug therapy is essential. Special attention should be given to side effects including diplopia or vertigo that may be considered normal phenomena by the family or the patient. Digestive disturbances, drowsiness or language expression disturbances should also be considered carefully. However, most adverse events are transitory and early discontinuation of a drug should be avoided in most cases, provided that the patient is informed beforehand and titration is slow. A moderate leukopenia and elevation of transaminases are common and do not herald the appearance of hepatic failure or pancytopenia.

In evaluating the efficacy of any drug regimen, clinical judgement based on seizure recurrences is fundamental. It is relatively easy in patients with frequent, regularly repeated seizures (e.g. in absence epilepsy) but it becomes long and difficult in patients with rare seizures or irregular seizures that cluster. This difficulty must not lead one to forget that the end-point of treatment is the control of seizures, not obligatorily a normal EEG or a so-called therapeutic blood level.

Monitoring the blood levels of AEDs is not routinely indicated and is rather useless in children with epilepsies that are well controlled on regular or low-dosage and well-tolerated monotherapy. Many patients are seizure-free with blood levels well below the published ranges, and modification of dosage to obtain ‘therapeutic’ levels is ineffective (Woo et al. 1988) and increases the risk of side effects. Likewise, discontinuation of a drug because its level is ‘subtherapeutic’ can result in seizure relapse (Richens 1982). Conversely, in resistant cases, the dose should be pushed to the limit of clinical tolerance, regardless of blood levels.

Blood level determinations may be useful to check patients’ compliance and to confirm suspected toxicity in infants or in children with intellectual disability, in whom recognition of a side effect may be difficult. Detection of blood interactions in patients taking multiple agents is less frequently required. Phenytoin therapy has a low therapeutic ratio (i.e. the margin of safety) which may lead to ‘breakthrough’ seizures in previously well-controlled children (Aicardi 1994). Blood levels are unhelpful with some drugs (vigabatrin, levetiracetam, lamotrigine, topiramate) and of dubious value with others, for example, sodium valproate, whose levels are poorly correlated to clinical effects.

Interpretation of blood levels is not always straightforward, especially in cases of interactions (Levy et al. 2002; Landmark et al. 2016); for drugs with variable protein binding that results in a change in levels of free, unbound, drug, and for those with active metabolites, such as carbamazepine, as the rate of formation of the metabolite is not constant and blood levels are not measured routinely.

When blood level determination is requested, should always consider the dose, time of administration and time of blood sample collection.

**ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS**

Adverse effects of antiepileptic drugs are common (Table 16.23) and extensive reviews are available (Levy et al. 2002; Kothare and Kaleyias 2007; Perucca and Gilliam 2012). The most common adverse effects are transient and occur at the beginning of treatment. These include digestive disturbances, drowsiness and dizziness. All antiepileptic agents may – albeit rarely – produce adverse effects that seriously hamper the patient’s activities. These effects range from acute intoxication with disturbances of consciousness (Larrieu et al. 1985; Zaret and Cohen 1986; Weaver et al. 1988; Meador 1994, 2001; Martin et al. 1999) or, exceptionally, death (Stone and Lange 1986; Murphy et al. 1987; Leestma et al. 1997) to subtle chronic toxicity with protein manifestations (McLeod et al. 1978; Dravet et al. 1980; Joyce and Gunderson 1980; Karas et al. 1982; McLachlan 1987; Pellock 1987; Appleton et al. 1990; Weig and Pollack 1993; Gerber et al. 2000; Pellock 2017b), and to apparently minor but sometimes psychologically and socially disabling effects such as acne, excessive weight gain (Egger and Brett 1981; Dinesen et al. 1984; DeToledo et al. 1997) or weight loss (Potter et al. 1997).

Allergic or idiosyncratic reactions are also common, and these may rarely be responsible for fatalities (Ghilus and Matte 1986; Browne et al. 1988; Kaufman et al. 1997; Schlienger et al. 1998; Fernández-Calvo et al. 2000).

Based on the underlying mechanisms, idiosyncratic reactions can be differentiated as follows:

1. Immune-mediated hypersensitivity reactions, which range from benign skin rashes to serious conditions such as drug-related rash with eosinophilia and systemic symptoms.
2. Reactions involving unusual nonimmune-mediated individual susceptibility, often related to abnormal production or defective detoxification of reactive cytotoxic metabolites (as in valproate-induced liver toxicity).
3. Off-target pharmacology, whereby a drug interacts directly with a system other than that for which it is intended, an example being some types of AED-induced dyskinesias.

Although no AED is free from the potential of inducing idiosyncratic reactions, the magnitude of risk and the most
<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Severe toxicity</th>
<th>Drug</th>
<th>Side effects</th>
<th>Severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Diplopia, Dizziness, Ataxia, Nausea,</td>
<td>Orofacial dyskinesia, Cardiac</td>
<td>Perampanel</td>
<td>Behavioural effects (agression, hostility, irritability, anger)</td>
<td>Fatigue</td>
</tr>
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<td></td>
<td>Hyponatraemia, Rashes (5–10%)</td>
<td>arrhythmia, Hepatotoxicity</td>
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<td></td>
<td></td>
<td>Pseudolymphoma</td>
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<tr>
<td>Clonazepam/clobazam</td>
<td>Fatigue, Ataxia, Hyperkinetic,</td>
<td>Psychosis, Thrombocytopenia</td>
<td>Phenobarbitone</td>
<td>Drowsiness, Agression, Sleep</td>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td>Aggression, Drowsiness, Hypersalivation, Bronchorrhoea, Muscle weakness</td>
<td></td>
<td></td>
<td>disturbances</td>
<td>Stevens–Johnson syndrome</td>
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<td></td>
<td>Rheumatism</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>Drowsiness, Dizziness, Blurred vision,</td>
<td>Prolongation PR interval;</td>
<td>Phenytoin</td>
<td>Ataxia, Anorexia, Nausea, Acne,</td>
<td>Orofacial dyskinesia, Anemia,</td>
</tr>
<tr>
<td></td>
<td>Incoordination, Hyponatraemia (&lt;2%),</td>
<td>not be given with</td>
<td></td>
<td>Nystagmus, Gum hypertrophy, Anchutism,</td>
<td>Lupus-like syndrome,</td>
</tr>
<tr>
<td></td>
<td>Rash (3%)</td>
<td>oxtcarbazepine as the</td>
<td></td>
<td>Megaloblastic anaemia, Osteomalacia,</td>
<td>Pseudolymphoma</td>
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<tr>
<td></td>
<td></td>
<td>combination can lead to</td>
<td></td>
<td>Reduced IgA, Depression, Neuropathy</td>
<td>Stevens–Johnson syndrome,</td>
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<tr>
<td></td>
<td></td>
<td>neurotoxicity</td>
<td></td>
<td></td>
<td>Hepatitis</td>
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<td></td>
<td></td>
<td></td>
<td>Encephalopathy</td>
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<tr>
<td>Ethosuximide</td>
<td>Anorexia, Nausea, Vomiting, Drowsiness,</td>
<td>Lupus-like syndrome,</td>
<td>Primidone</td>
<td>Drowsiness, Dizziness, Nausea, Vomiting,</td>
<td>Agranulocytosis, Lupus-like</td>
</tr>
<tr>
<td></td>
<td>Headache, Hiccups, Rashes</td>
<td>Aplastic anaemia, Psychosis</td>
<td></td>
<td>Personality change, Diplopa, Ataxia,</td>
<td>syndrome, Thrombocytopenia</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Drowsiness, Nausea, Hepatic failure</td>
<td>Aplastic anaemia (can be lethal)</td>
<td>Rufinamide</td>
<td>Somnolence, Vomiting, Anorexia, Weight Loss</td>
<td>QTC interval shortening can occur, although complications are rare</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Headache, Dizziness</td>
<td>None</td>
<td>Sodium valproate</td>
<td>Anorexia, Nausea, Vomiting, Hair loss,</td>
<td>Hepatotoxicity (see also Chapter 9 on Metabolic Disorders)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight gain, Tremor, Drowsiness,</td>
<td>Teratogenicity (see text)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia, Hyperammonoaemia (usually mild)</td>
<td>Pancreatitis, Stupor, encephalopathy</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Dizziness, Diplopia, Nausea, Headache</td>
<td>Hypersensitivity to LCM as acute angioedema (very rare)</td>
<td>Topiramate</td>
<td>Loss of appetite, Weight loss, Slurring of speech, Difficulty concentrating</td>
<td>None</td>
</tr>
</tbody>
</table>
common manifestations vary between drugs, a consideration that impacts on treatment choices (Zaccara et al. 2007).

**Antiepileptic Drugs and Cognition**

The cognitive effects of anticonvulsants (Meador 1994, 2001; Aldenkamp 2001; Boshuisen et al. 2015) must also be carefully monitored, and no drug is completely exempt from unfavourable cognitive or behavioural effects. Some agents (e.g. phenobarbitone, topiramate) are more prone to adverse effects than others (e.g. sodium valproate, carbamazepine, lamotrigine, gabapentin, levetiracetam).

The relative effects of the newer AEDs are not fully determined. No cognitive effects were found with lamotrigine (Smith et al. 1993), and several studies using quality-of-life measures reported a beneficial effect of lamotrigine on patient perception of psychological well-being (Smith et al. 1993; Brodie et al. 1995). In 25 healthy adults participating in a double-blind randomised crossover design study, lamotrigine produced significantly fewer cognitive and behavioural effects than carbamazepine (Meador 2001). Psychomotor slowing, language problems and memory disturbance are reported with topiramate (Martin et al. 1999; Bootsma et al. 2006). Word-finding difficulty in both children and adults is unique to topiramate (Meador 2001; Brandt et al. 2015).

Witt et al. (2015) demonstrated greater adverse effects of a higher drug load on cognition, especially executive functions. We share the conclusion of the authors that ‘simply counting the number of drugs may be sufficient as a rough estimate of the risk of side effects’. Despite available data it is unfortunately still common to see children, particularly with severe epileptic encephalopathies, treated with four or more irrationally associated AEDs. This practice may intensify the consequences of the underlying pathology and rarely leads to a clinically meaningful reduction of seizure frequency.

Neuropsychological testing is helpful to identify cognitive adverse effects that severely impair quality of life. Cognitive screening can be achieved by easy-to-use scales such as EpiTrack, a 15-minute tool to detect and track cognitive side effects of AEDs and adverse effects of seizures (Lutz and Helmstaedter 2005). A junior version of EpiTrack is a valid and reliable screening tool for assessing executive function in children and adolescents (Helmstaedter et al. 2010).

**ANTIEPILEPTIC DRUGS AND PREGNANCY RELATED ISSUES**

Teratogenicity must be considered with long-term treatment for female adolescents with epilepsy (Morrell 2002; Tetenborn et al. 2002). AEDs are among the most common teratogenic drugs and induce both anatomical (malformations) and behavioural (cognitive/behavioural) changes in the offspring (Meador and Loring 2016). Treating epilepsy during pregnancy requires a balance between maternal and fetal risks associated with uncontrolled seizures against the potential teratogenic effects of AEDs. A rational approach requires knowledge of these risks, an understanding of the effects of pregnancy on seizure control and AED disposition (Battino and Tomson 2007). Older AEDs (benzodiazepines, phenytoin, phenobarbital and valproate) carry a risk of major fetal malformations, including cleft lip and palate and cardiac defects.

The International Registry of Antiepileptic Drugs and Pregnancy (EURAP), prospectively epilepsy and pregnancy registry prospectively monitored pregnancies exposed to monotherapy with different doses of four common drugs: carbamazepine, lamotrigine, valproic acid, or phenobarbitral (Tomson et al. 2011). Pregnancies were excluded if they ended in spontaneous abortions, had chromosomal or genetic abnormalities, involved treatment changes in the first trimester or other situations that could affect fetal outcome. The authors assessed rates of major congenital malformations in 1402 pregnancies exposed to carbamazepine 1280 to lamotrigine 1010 to valproic acid, and 217 to phenobarbitral. An increase in malformation rates with increasing dose at the time of conception was recorded for all drugs. Multivariable analysis including ten covariates in addition to treatment with AEDs showed that the risk of malformations was greater with a parental history of major congenital malformations (odds ratio 4.4, 95% confidence intervals 2.06–9.23).
The lowest malformation rates occurred with less than 300mg per day lamotrigine [2.0% (17 events), 95% confidence intervals 1.19–3.24] and less than 400mg per day carbamazepine [3.4% (five events), 95% confidence intervals 1.11–7.71]. Compared with lamotrigine monotherapy at doses less than 300mg per day, risks of malformation were significantly higher with valproic acid and phenobarbital at all investigated doses, and with carbamazepine at doses greater than 400mg per day (Tomson et al. 2011).

The UK Epilepsy and Pregnancy Register (Morrow et al. 2006) showed that only 4.2% of live births to women with epilepsy had a major congenital malformation (MCM). The MCM rate for multi-drug exposure was greater than for monotherapy. Multi-drug regimens containing valproate had significantly more MCMs. Carbamazepine monotherapy was associated with the lowest risk of MCM (Morrow et al. 2006).

The risk of malformations is generally regarded as highest in fetuses exposed to multiple AEDs in higher doses. The majority of patients with epilepsy maintain seizure control during pregnancy. Seizure control and AED treatment were recorded prospectively in 3806 pregnancies of 3451 women with epilepsy taking part in EURAP (Battino et al. 2013); 66.6% remained seizure-free throughout pregnancy. Generalised tonic–clonic seizures occurred in 15.2% and women with idiopathic generalised epilepsy were more likely to remain seizure-free (73.6%) than women with localisation-related epilepsy (59.5%; P<0.0001). Worsening of seizure control from the first to second or third trimesters occurred in 15.8% of pregnancies. The AED dose was increased during pregnancy in 26.0% and a second AED added to the initial monotherapy in 2.6% of pregnancies. Seizures were more likely to occur in the first trimester in pregnancies with a greater drug load (35%; increased dose and/or addition of another AED) than in pregnancies without an increase (15.3%) (P<0.0001). Pregnancies exposed to lamotrigine were less likely to be seizure-free, 58.2% (P<0.0001), had more generalised tonic–clonic seizure (GTCS) (21.1%; P<0.0001) had a greater likelihood of diminished seizure control from first to second or third trimesters (19.9%; P<0.01), and were more likely to require an increase in drug load, 47.7% (P<0.0001). The authors concluded that a more proactive approach to adjusting the dose of AEDs in pregnancy should be considered, in particular in pregnancies with seizures in the first trimester and exposure to lamotrigine (Battino et al. 2013).

Congenital malformations associated with AEDs are generated in the first trimester of pregnancy and neural tube defects are complete by day 28 after conception. Pre-conception counselling is thus essential. Modifications of the ongoing treatment should take place before conception to allow optimal therapy with the lowest possible dose, preferably of monotherapy. The type(s) of seizures must be taken into account. For example, if generalised tonic–clonic seizures in a patient with JME are well controlled with an average dose of lamotrigine but some myoclonic jerks persist, not adding other medication, at least until the end of the first trimester, is preferable.

**ANTIEPILEPTIC DRUGS AND A PARADOXICAL INCREASE IN SEIZURE FREQUENCY**

In some cases, AEDs cause a paradoxical increase in seizure frequency (Guerrini et al. 1998a, 2002c; Perucca et al. 1998). Carbamazepine, vigabatrin or gabapentin are contra-indicated in patients with absence epilepsy or juvenile myoclonic epilepsy (Shorvon et al. 1978; Callahan and Noetzel 1992) and should be used with caution in patients with a mixed seizure disorder, particularly in combination of atonic, tonic–clonic, myoclonic and atypical absence seizures with generalised EEG discharges (Perucca et al. 1998). Aggravation of seizures is reported with lamotrigine in young children with Dravet syndrome (Guerrini et al. 1998b). The aggravation of absence or myoclonic seizures with phenytoin has also been reported, but the overall number of cases is lower than that recorded with carbamazepine.

In view of the problems associated with chronic treatment with AEDs, much depends on cooperation between patient and his or her family and their understanding of the problems posed by the disorder. The nature of the problem should be explained in simple terms, and the need for prolonged supervision should be emphasised. Treatment is a reasonable compromise between when initiating anticonvulsant medication that modifying the dosage to find the best dose for the individual child is often necessary, and that different or additional medications may be required if the first drug fails to control seizures. This may help parents to accept later changes with less anxiety and fewer doubts about the competence of their physician.

**NON-DRUG MEDICAL TREATMENTS**

**KETOCENIC DIET**

The ketogenic diet has long been in use for the treatment of children with severe epilepsies (Freeman et al. 2007). Although the mechanism of action of the diet is poorly understood (Boison 2017), a high serum concentration of ketone bodies is required for its effectiveness. Various modifications of ketogenic diets utilise either medium-chain triglycerides or conventional 4:1 or 3:1 ratios. Although unpalatable, the diet’s taste and appearance can be made acceptable (Freeman et al. 1994). Side effects include diarrhoea, growth failure and, in some children, renal stones and severe acidosis. These may be life-threatening, and fatalities have occurred, especially with the co-administration of acetazolamide (Prasad et al. 1996). This drug should therefore be discontinued two weeks before...
starting the diet. Elevated levels of cholesterol are occasionally observed, and long-term effects are poorly documented. The short-term beneficial effect of the diet is indisputable for several types of seizures including myoclonic seizures (Caraballo et al. 2006), the LGS (Schwartz et al. 1989a, b) and some resistant focal or generalised seizures (Kossoff et al. 2006).

The 2016 Cochrane review (Martin et al. 2016) identified seven randomised controlled trials that generated eight publications (Bergqvist et al. 2005; Kossoff et al. 2007; Seo et al. 2007; Neal et al. 2008, 2009; Raju et al. 2011; El-Rashidy et al. 2013; Sharma et al. 2013). All applied intention-to-treat analysis with varied randomisation methods. The seven studies recruited 427 children and adolescents and no adults. A meta-analysis could not be conducted due to the heterogeneity of the studies. Reported rates of seizure freedom were as high as 55% in a 4:1 ketogenic diet group after 3 months and seizure reduction reached 85% in a 4:1 ketogenic diet group after 3 months.

Adverse effects occurred in all studies and for all ketogenic diet variations, including short-term gastrointestinal-related disturbances, to longer-term cardiovascular complications. Attrition rates were reported with all ketogenic diets and across all studies due to lack of observed efficacy and dietary tolerance.

At the initiative of The Charlie Foundation, a panel comprised of 26 paediatric epileptologists and dietitians from nine countries with expertise in the ketogenic diet published a set of clinically useful recommendations (Kossoff et al. 2009). Based on available data the panel agreed on a list of syndromes and conditions in which the ketogenic diet is beneficial including glucose transporter protein 1 (GLUT-1) deficiency, pyruvate dehydrogenase deficiency (PDHD), myoclonic–astatic epilepsy, tuberous sclerosis complex, Rett syndrome, Dravet syndrome, epileptic infantile spasms, selected mitochondrial disorders, glycogenosis Type V, Landau–Kleffner syndrome, Lafora body disease and subacute sclerosing panencephalitis. The authors also listed a set of disorders with an absolute contraindication to the use of ketogenic diet including carnitine deficiency (primary), carnitine palmitoyl transferase (CPT) I or II deficiency, carnitine translocase deficiency; several β-oxidation defects, pyruvate carboxylase deficiency and porphyria (Kossoff et al. 2009).

Education of parents is all important and a team approach is essential for optimal results (Kossoff et al. 2007). Consideration should be given to discontinue the ketogenic diet after 3 months if unsuccessful, and 2 years if completely successful, but longer diet durations are necessary for GLUT-1 and PDHD and may be perfectly appropriate based on individual responses for intractable epilepsy. During discontinuation, the group recommended a gradual wean over 2–3 months, unless an urgent discontinuation of the diet is indicated.

For a long time, the ketogenic diet was not recommended for use in infancy (under the age of 2 years) because it is a crucial period in development and the perceived high risk of nutritional inadequacies. For a consensus statement regarding guidelines for the clinical management of the ketogenic diet in infants see Van der Louw et al. (2016).

**SURGICAL TREATMENT OF EPILEPSY**

Although approximately 70% of patients respond satisfactorily to drugs, resistant cases especially in children are not rare. A sizeable number of these can potentially be controlled by surgical treatment, as shown by experience in adults. Paediatric surgical data are also encouraging and no different from the adult surgical outcome data (Lindsay et al. 1979; Gilliam et al. 1997; Wyllie et al. 1998; Mathern et al. 1999; Bittar et al. 2002; Schmidt et al. 2004). Successful surgical therapy is particularly desirable for children and deserves to be considered more liberally and earlier than is now customary (Engel 1996; Aicardi 1997; Arzimanoglou et al. 2004; Cross et al. 2006, 2016). It would constitute a definitive treatment, not only preventing the possible harmful consequences on the brain of repeated seizures and the psychosocial problems resulting from interference of epilepsy with everyday life and education, but also by permitting the use of smaller dosages for AEDs or even their discontinuation (Aicardi 1997). In spite of these potential advantages, the utilisation of epilepsy surgery in children remains underutilised (Lachhwani 2005; Arzimanoglou et al. 2016c). Although epilepsy surgery programmes have been launched in most major paediatric centres, the interval between onset of the disease and surgery is still extremely long, often more than 15 or 20 years. Unfortunately, such delays occur even for well-defined epilepsy syndromes such as mesiotemporal epilepsy (Berg et al. 2003). In one randomised controlled trial, Wiebe et al. (2001) compared surgical versus medical treatment for temporal lobe epilepsy in adults, showing that seizure control and quality of life were significantly better with surgery than with medical treatment.

Multiple historical features suggest a low likelihood of seizure remission. Most are recognisable early in the course of treatment and the threshold for referring children for further evaluation should be low (Table 16.24). Childhood-onset epilepsy differs significantly from adult-onset cases as several aetiologies and syndromes are unique to the paediatric population. For many, the aetiology only becomes clear as the epilepsy evolves, thus the history obtained by the clinician must include a detailed description of seizure onset, such that idiopathic epilepsies of childhood which ultimately remit or those of symptomatic genetic origin (i.e., *SCN1A* mutations) which are unlikely to benefit from surgical therapy are correctly identified. At the same time, there are several paediatric epilepsy syndromes and aetiologies in which surgical therapy is especially efficacious and should be considered early in the course of treatment. Lastly, infants and young children differ in that catastrophic epilepsy presentations may require more urgent surgical evaluation to prevent epileptic encephalopathy and loss of neurodevelopmental status.

The most obvious and probably still strongest barriers to surgery are cultural and psychological (Jetté et al. 2016; 

Chapter 16  Epilepsy and Other Seizure Disorders

Kwon et al. 2016. Information on surgical options are under-appreciated by general practitioners and even neurologists and child neurologists. The decision-making processes are usually highly complex and require a multidisciplinary approach involving input from several specialties and specialised diagnostic procedures (Arzimanoglou et al. 2016c). Lack of knowledge, concern or outright fear regarding surgery may also lead to protracted delay. A rollercoaster course characterised by remission and exacerbation may also render it difficult to know if the epilepsy is truly drug resistant (Berg et al. 2006). Additional confounding factors include the poorly known natural history of many childhood epilepsies, varied aetiologies, and the fact that studies may bundle together lesional and atrophic lesions. Given the lack of class 1 or 2 evidence for AEDs (see Adverse Effects of Antiepileptic Drugs section). Consequently, multiple AED trials in children who are favourable surgical candidates are likely to be futile (Lachhwani 2005). New drug regimens not only delay definitive surgical procedures but increase morbidity (and mortality) from ongoing seizures, and compromise cognitive development (Vasconcellos et al. 2001; Nolan et al. 2003; Aldenkamp et al. 2005; Laurent and Arzimanoglu 2006) and long-term adverse effects of AEDs (see Adverse Effects of Antiepileptic Drugs section).

Another major step that facilitated early access to surgery has resulted from the development of new and powerful neuroimaging techniques (MRI, PET, SPECT, fMRI, MEG) that facilitate precise definition of the type and operability of epileptogenic lesions. Given the lack of class 1 or 2 evidence for the relative utility of each modality, recommendations were issued by a consensus of the Paediatric Epilepsy Surgery Task Force of the ILAE Commissions of Pediatrics and Diagnostics (Jayakar et al. 2014). The recommendations limit over or underutilisation while retaining substantial flexibility in the use of the tests.

Further development of video-EEG techniques and intracranial electrodes and employment of neurosurgical tools and techniques (Jayakar et al. 2016; Tassi et al. 2016), also contributed to the change of views regarding epilepsy surgery in children. For example, epilepsies formerly considered generalised may indeed be due to localised lesions which may be amenable to surgery. This applies, for example, to many cases of epileptic infantile spasms and possibly to other syndromes with diffuse or multifocal features (Madhavan et al. 2007). Epilepsy surgery may be successful for selected children and adolescents with a congenital or early-acquired brain lesion, despite abundant generalised or bilateral epileptiform discharges on EEG (Wyllie et al. 2007).

<table>
<thead>
<tr>
<th>Aetiologies which are unlikely to benefit from surgical therapy</th>
<th>Clinical findings</th>
<th>Recommended testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome (severe myoclonic epilepsy of infancy)</td>
<td>Frequent/prolonged febrile seizures in infancy</td>
<td>SCN1A gene testing</td>
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<tr>
<td>Epilepsy and intellectual disability limited to females</td>
<td>Frequent febrile seizures as infant</td>
<td>PCDH19 gene testing</td>
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<tr>
<td>CDKL5 syndrome</td>
<td>Early onset infantile spasms</td>
<td>CDKL5 gene testing</td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>Early childhood focal seizures in non-REM sleep</td>
<td>CHRNA4, CHRNB2, CHRNA2 gene testing</td>
</tr>
</tbody>
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Aetiologies in which surgical therapy may be considered a treatment of choice

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical findings</th>
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<tbody>
<tr>
<td>Low-grade cortical tumours</td>
<td>Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>Hemimegalencephaly</td>
</tr>
<tr>
<td>Focal cortical dysplasias</td>
<td>Rasmussen encephalitis</td>
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<tr>
<td>Hypothalamic Hamartoma</td>
<td>Tuberous sclerosis complex</td>
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*For a detailed description of surgical treatment of the epilepsies per aetiology refer to Arzimanoglu et al. (2016).*
INDICATIONS, CONTRAINDICATIONS AND TYPES OF AVAILABLE SURGICAL TREATMENT

Most surgical techniques are intended to remove the epileptogenic tissue responsible for initiation and spread of the seizure discharge. Criteria for surgical removal of epileptogenic tissue include a severity sufficient to interfere with everyday life, cognitive deterioration related to active epilepsy, clinical and other evidence pointing to a localised brain area, and the possibility of removing epileptogenic tissue without unacceptable functional sequelae.

Several procedures are utilised to treat epilepsy. These can be schematically grouped into two major categories:

1. Excisional surgery that removes the cortical neuronal pool responsible for generation of the seizures; and
2. Palliative or functional surgery, which aims to interrupt or limit the propagation of seizure discharges, thus limiting their clinical manifestations and consequences.

Excisional surgery includes a wide spectrum of procedures including small cortical resections to hemispherectomy. Palliative surgery (Polkey 2003a) is mostly represented by callosotomy, whether of the anterior half or two-thirds of this structure or complete (Jalilian et al. 2010).

Other palliative techniques include vagus nerve stimulation (VNS), which requires placement of a stimulator under the skin. In this technique, an electrode is wrapped around the left vagus nerve, so that adjustable pulsed stimuli can be applied. In children, the results are encouraging with reduced seizure frequency, particularly in the epileptic encephalopathies (Polkey 2003a, b; Alexopoulos et al. 2006; Benifla et al. 2006; Panebianco et al. 2015; Lagae et al. 2016), but controlled studies are still lacking. Adverse effects associated with implantation and stimulation are primarily hoarseness, cough, dyspnoea, pain, paraesthesia, nausea and headache, with hoarseness and dyspnoea more likely to occur with high than low stimulation.

The long-term impact of VNS was discussed in a retrospective multicentre study of 347 children aged 6 months to 17.9 years at the time of implant (Oroz et al. 2014). The results indicated that at 6, 12, and 24 months after implantation, 32.5%, 37.6%, and 43.8%, respectively, of patients experienced a ≥50% reduction in baseline seizure frequency of the predominant seizure type. Responder rates were higher in a subgroup of patients who had no change in AEDs during the study. Favourable results were also evident for all secondary outcome measures including changes in seizure duration, ictal severity, postictal severity, quality of life, clinical global impression of improvement, and safety. Post-hoc analyses demonstrated a statistically significant correlation between VNS total charge delivered per day and an increase in response rate (Oroz et al. 2014). No new safety issues were identified.

Implantation of a VNS is indicated as adjunctive therapy in children with focal epilepsies, who for any reason are not good candidates for surgical treatment. Children with predominantly generalised seizures from genetic, structural epilepsies, like Dravet syndrome or LGS also benefit from VNS therapy.

Gamma-knife radiosurgery in the treatment of cortical–subcortical cavernous angiomas and hypothalamic hamartomas may be an option for well selected patients (Régis et al. 2007). Another technique that is still experimental, almost exclusively in adult patients, is deep brain stimulation (Chabardes et al. 2002; Benabid et al. 2003), the results of which are still too recent to draw conclusions.

The majority of candidates for epilepsy surgery, in both children and adults, belong to the syndromic category of focal structural (non-idiopathic epilepsies) (Kahane et al. 2005). However, while some syndromes are amenable to surgical intervention, others are unlikely to respond favourably (Table 16.25). The requirements for resective surgery in children with focal epilepsy vary with the type of resection considered. Three basic requirements apply to almost all cases: (1) the epileptogenic area must be clearly localised to a restricted brain region; (2) no other independent epileptogenic area exists in those areas that are not included in the planned resection, and (3) any possible deficit resulting from resection must be acceptable (Arzimanoglou et al. 2004).

Completeness of resection of the epileptogenic area is the major condition for a satisfactory surgical result. The choice of procedure depends upon the location and extent of the ictal onset zone, its relationship with adjacent functional brain areas and convergent data that confirms the surgical target. Epilepsy surgery mandates a multidisciplinary approach that

<table>
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<th>Table 16.25</th>
<th>Historical features which predict evolution to intractable epilepsy</th>
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<tr>
<td>History of multiple seizure types</td>
<td>(Kwong et al. 2003; Altunbasek et al. 2007)</td>
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<tr>
<td>History of infantile spasms</td>
<td>(Berg et al. 1996; Kwong et al. 2003)</td>
</tr>
<tr>
<td>Onset of seizures in infancy</td>
<td>(Chevrie and Aicardi 1979; Casetta et al. 1999)</td>
</tr>
<tr>
<td>Remote symptomatic aetiology</td>
<td>(Berg et al. 1996; Casetta et al. 1999)</td>
</tr>
<tr>
<td>Abnormal neurological examination</td>
<td>(Chevrie and Aicardi 1979; Kwong et al. 2003)</td>
</tr>
<tr>
<td>Frequent seizures (daily/weekly) prior to treatment</td>
<td>(Casetta et al. 1999; Kwong et al. 2003)</td>
</tr>
<tr>
<td>Early recurrence of seizures (within 6–12 months of treatment)</td>
<td>(Kwong et al. 2003)</td>
</tr>
<tr>
<td>History of status epilepticus prior to diagnosis</td>
<td>(Berg et al. 1997; Kwong et al. 2003; Altunbasek et al. 2007)</td>
</tr>
<tr>
<td>History of neonatal seizures</td>
<td>(Berg et al. 1997; Altunbasek et al. 2007)</td>
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<tr>
<td>Intellectual disability (Altunbasek et al. 2007)</td>
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<tr>
<td>Seizure clustering</td>
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</table>
requires considerable experience and technologically sophisticated procedures. A comprehensive assessment of risks and benefits is always required. All decisions require close collaboration between the epilepsy team, the patient and the family. With the presurgical investigations should be decided on an individual basis (Engel 1993, 1996; Tuxhorn et al. 1997; Lüders and Comair 2001).

The clinical expression of epilepsy may be misleading in children as generalised seizures may have a focal onset. The surgical spectrum in early-onset epilepsy now includes not only other focal epilepsies but also more complex secondarily generalised types. Developmental lesions that cause infantile epilepsy are often poorly localised, involve extensive brain areas and require extensive operations (e.g. hemispherotomy). Surgery is also performed in progressive conditions such as tuberous sclerosis (Jansen et al. 2007).

**PRESURGICAL EVALUATION OF CHILDREN**

Presurgical evaluation has the same bases in children as it does in adults. Detailed consideration of the existing methods is beyond the scope of this book, and the reader is referred to the extensive literature available (e.g. Lüders and Comair 2001; Kahane et al. 2005; Arzimanoglou et al. 2016c).

The presurgical assessment of a patient is a stepwise process. Detailed history taking and precise definition of the clinical seizure pattern (in terms of both symptoms and sequence of events) are indispensable. The importance of the EEG has been repeatedly emphasised. In some lesional cases ictal EEG and high-quality structural neuroimaging may prove sufficient for localisation. More often in both lesional and MRI-negative cases, video-EEG recording is essential. Congruence among the results of the clinical history and the definition of seizure pattern, the neuropsychological evaluation and neuroradiology, scalp EEG (interictal and ictal), and, in selected cases, other supporting tests (e.g. ictal or interictal SPECT and PET, functional MRI) should be sought as any discordance in the results of the various investigation methods considerably decreases the chances of a good outcome. Intracranial EEG recording remains the criterion standard for the localisation and definition of the extent of the epileptogenic zone, particularly for MRI-negative cases or when the limits of the lesion cannot be clearly identified by structural neuroimaging. The method of intracranial study (grids, strips, stereotactically implanted depth electrodes) depends on the pre-operative hypothesis and experience of the epilepsy surgery team.

EEG recording, functional imaging and ictal semiology are analysed to evaluate children with MRI-negative focal epilepsy. All of these factors are influenced by maturation, and the potential for significant changes over time must always be considered. This is especially evident in infants whose symptomatic focal epilepsy is more likely to propagate to motor pathways leading to apparent electro-clinically generalised epileptic seizures (Duchowny 1987). Surgically remediable cases of MRI-negative infantile spasms have been reported, and a high frequency of infantile spasms tuberous sclerosis complex evolves into focal epilepsy (Riikonen and Simell 1990).

Systematically, all available data must be reviewed and analysed by an experienced multidisciplinary group.

**MRI-Negative Patients**

The importance of MRI in the pre-operative evaluation for epilepsy surgery cannot be overestimated. Utilising high-resolution epilepsy protocols and expert interpretation, MRI detects structural lesions in up to 85% of MRI-negative patients (van Oertzen et al. 2002). The presence of a focal lesion helps define the epileptogenic zone and guides placement of intracranial electrodes. In a recent review of current practice worldwide (Harvey et al. 2008), MRI was performed in 99.5% of paediatric epilepsy surgical candidates.

In contrast, the inability to detect a focal lesion on MRI presents significant challenges to the successful localisation of the epileptogenic zone. Histopathological analysis of tissue removed in MRI-negative cases often reveals microscopic abnormalities. The incidence of MRI-negative cases in the ILAE taskforce series was 17% (Harvey et al. 2008), although meta-analysis of patients of all ages reveals a considerably higher incidence of magnetic resonance negativity in the paediatric population (31% in children versus 21% in adults) (Telléz-Zenteno et al. 2010). Referral bias is undoubtedly important as centres with experience in invasive EEG recording techniques have an incidence of MRI-negative cases that is over 50% (Paolicchi et al. 2000).

All children with refractory MRI-negative focal epilepsy should first undergo video/EEG recording with ictal capture. If a focal region of epileptogenesis is identified, MRI re-investigation with a focus on a specific region of interest should be performed. Ideally, the epileptogenic region should be convergent with the semiotically suspect anatomical region of seizure onset. Particular attention must be given to focal electrographic features at seizure onset as these are highly relevant to the identification of the zone of seizure origin.

The role of functional imaging in paediatric cases is well established. Ictal SPECT and PET are both sensitive and specific tools to delineate temporal and extratemporal seizure-onset zones (Gaillard et al. 1995; Lawson et al. 2000; Kaminska et al. 2003; Juhasz and Chugani 2003). Functional imaging is not always required in MRI-negative patients, but is helpful when there is a lack of clinical and electrophysiological convergence. In contrast, functional imaging is virtually obligatory in divergent and MRI-negative cases. Although ictal SPECT is considered superior for localising extratemporal foci and PET superior for temporal foci, a comparison of both modalities in paediatric temporal lobe epilepsy reveals diagnostic accuracy in the range of 80–90% for both (Lee et al. 2005).

More recently, MEG has been employed successfully in MRI-negative cases. In a cohort of 22 children with subtle
or nonfocal MRI findings, RamachandranNair et al. (2007) identified 17 (77%) with good surgical outcome and eight (36%) who became seizure-free. Postoperative seizure-free dominance correlated with the presence of MEG clusters within the resection margin whereas bilateral MEG dipole clusters or scattered dipoles correlated with seizure persistence. Seizure-freedom was greater when there was complete concordance between MEG and EEG localisation. Multiple seizure types predicted poor postoperative outcome.

The use of multiple modalities to define the epileptogenic zone in MRI-negative paediatric refractory focal seizures is widely regarded as state-of-the-art (Kurian et al. 2007; Seo et al. 2007; Jayakar et al. 2008; Dorward et al. 2011). The choice of modality depends on local institutional protocols and resources, and there is only limited data to support the superiority of a single approach.

In a study of 14 children undergoing comprehensive multimodal investigations for intractable MRI-negative focal epilepsy, SISCOM (subtraction fctal SPECT co-registered to MRI) and MEG showed better concordance with intracranial EEG data than PET (Seo et al. 2007). However, PET and SPECT data do not guarantee a seizure-free outcome (Dorward et al. 2011). It is difficult to draw definitive conclusions when the number of patients is limited.

The existing evidence indicates that favourable outcomes are indeed possible and that rates of seizure-freedom are comparable to adults. Low-grade focal cortical dysplasia is the underlying pathology in the majority of candidates, but a seizure-free outcome is pathology-independent as it is determined by the ability to completely excise the physiological and anatomical seizure-onset zone. This goal is achievable in many children with a multimodal approach. The number of children with refractory focal epilepsy who are MRI-negative but are not referred for surgical consideration is unknown.

OUTCOME OF SURGICAL THERAPY

Complete resection of the epileptogenic zone as a predictor of seizure-free outcome is singularly important and has been characterised by complete resection of the anatomical lesion by MRI and complete resection of the epileptogenic zone as defined by intracranial recordings. Krsek et al. (2009) found that 70% of patients became seizure-free following complete resection of the epileptogenic zone as defined by both anatomical and physiological resection, while only 22% of patients with incomplete resection achieved seizure-freedom. However, complete resection of the epileptogenic zone by EEG or MRI when complete resection by both modalities is not possible may also achieve seizure-freedom (Perry et al. 2010).

In a retrospective review of incomplete resections in children characterised by both EEG and MRI completeness, 40% achieved seizure-freedom, with those incomplete by both MRI and EEG least likely to become seizure-free (24%) compared to over 50% incomplete by one modality (Perry et al. 2010). These findings confirm that complete resection of EEG and MRI abnormalities is the best predictor of a seizure-free outcome, but a seizure-free outcome is still attainable with complete resection by at least one modality. The contribution of each modality to the concept of complete resection is debated, with some data suggesting an advantage to complete EEG resection over complete MRI resection (Perry et al. 2010).

Several other variables contribute to seizure-freedom to a lesser degree, many ultimately related to the ability to achieve complete resection. Among pre-operative variables, unifocal lesions on pre-operative MRI have more favourable outcome (Cossu et al. 2008; Perry et al. 2010). Widespread lesions on MRI may limit the ability to achieve complete resection. Other pre-operative variables such as age of seizure onset and duration of epilepsy prior to surgery do not impact outcome (Kral et al. 2003; Cossu et al. 2008; Krsek et al. 2009). Patient specific substrate may indirectly influence outcome in some cases. For example, a full scale IQ of less than 70 has been associated with poor postsurgical outcome as have psychiatric comorbidities in patients undergoing temporal lobectomy (Guarnieri et al. 2009; Kanner et al. 2009). Both suggest more widespread cerebral involvement that compromises the likelihood of a complete resection.

Of the operative variables, temporal lobe resection has repeatedly demonstrated better outcome (Wyllie, et al. 1998; Alexandre et al. 2006; Cossu et al. 2008), up to 70% at 5 years in some case series (Benifla et al. 2008). This finding may be related to less common overlap of the epileptogenic zone with eloquent cortex, as occurs commonly in extratemporal locations. Unilobar resections more commonly result in seizure-free outcome than multilobar procedures (Wyllie, et al. 1998; Cossu et al. 2008; Perry et al. 2010), a finding also likely related to completeness of resection.

Finally, histopathological variables may contribute to seizure-freedom outcome. Several series have demonstrated more favourable outcome when the aetiology of epilepsy is related to tumour versus cortical dysplasias (Wyllie et al. 1998; Cossu et al. 2008). Hamiwa et al. reported 72% seizure-free rates at 10 years in patients with developmental tumours versus 32% for cortical dysplasia. These findings likely reflect completeness of resection, as tumours are typically well circumscribed. Among patients with FCD, those with Type Ia/b more often achieve postsurgical seizure-freedom compared to those with Type Ia/b and mild malformation of cortical development (Krsek et al. 2009). Type II FCD is more easily detected by MRI, while lower grade FCD is more often diffuse and poorly localised.

PALLIATIVE EPILEPSY SURGERY

The primary surgical goal seizure-freedom for intractable epilepsy is not always achievable and seizure reduction is an alternative benefit in some candidates. Palliative procedures
may eliminate one of several seizure types. For example, eliminating atonic seizures reduces the risk of injury (e.g. fractures, lacerations). Similarly, eliminating complex partial seizures in temporal lobe epilepsy with continued auras without loss of consciousness may be tolerable and beneficial. Reducing the likeliness of status epilepticus or seizure clusters is also positive.

Corpus callosotomy is an effective treatment to reduce or eliminate atonic seizures. Other generalised seizure types such as myoclonic, absence, and tonic–clonic seizures are less likely to respond. Callosotomy disrupts the major trans-callosal pathway linked to rapid propagation of ictal discharges between the cerebral hemispheres. Partial callosal disconnection (anterior two-thirds) is often sufficient to achieve this goal while complete corpus callosotomy increases risk for the disconnection syndrome (Jalilian et al. 2010).

Multifocal cortical malformations or multifocal ictal onset zones may also benefit from palliative procedures. Patients with tuberous sclerosis complex exemplify this clinical scenario. The pre-operative evaluation must identify the epileptogenic tuber and epileptogenic potential of surrounding tubers. Outcome is generally favourable when the MRI, EEG and SPECT findings are convergent. In cases with multifocal ictal onset, resection of the region associated with the most debilitating seizure type or most frequent onset can prove beneficial (Radhakrishnan et al. 2008). In a recent review of Lennox–Gastaut cases undergoing excisional procedures, 74% experienced seizure-freedom or significant reduction of seizures at 33 months follow-up (Lee et al. 2010). The majority (85%) had cerebral lesions on MRI, although nonlesional patients also experienced benefit from surgical treatment.

Another commonly encountered indication for palliative surgery is the presence of ictal onset which encroaches upon eloquent cortex. As complete resection of the epileptogenic zone would result in unacceptable disability, sparing of eloquent cortex may result in significant improvement. When both the MRI defined lesion and EEG defined epileptogenic zone cannot be completely resected, the likelihood seizure-freedom is low. However, if at least one modality can be completely resected, seizure-freedom occurs in a clinically significant proportion of patients (Perry et al. 2010). This underscores the importance of including patients for epilepsy surgery in whom the pre-operative evaluation suggests the procedure may be incomplete.

Multiple subpial transections (MST) have been utilised for seizures arising within functional cortex. As functional cortical units are arranged radially while epileptogenic activity spreads horizontally a transverse cortical incision should theoretically disrupt horizontal spread while preserving radial functionality. When performed in conjunction with focal cortical resections MSTs can result in seizure reduction nearing 60%. However, when used alone, seizure-freedom rates are much more disappointing (Benifla et al. 2006).

**ANTIEPILEPTIC DRUGS FOLLOWING SURGERY**

Discontinuation of AED treatment should be considered in all children with postoperative seizure-freedom but should follow assessment of risks and consequences of seizure recurrence (Braun and Schmidt 2014; Braun et al. 2016). Seizure recurrence following postoperative AED withdrawal is between 15% and 30%, with children being less at risk than adults.

There is no proof that AED withdrawal itself negatively affects long-term seizure outcomes in seizure-free patients under AED treatment or after epilepsy surgery. AED discontinuation only unveils the natural history of the epilepsy and the completeness of resection after epilepsy surgery (Boshuisen et al. 2012, 2014). This was convincingly demonstrated by an observational retrospective study (TimeToStop) of 766 children under age 18 years from 15 European centres. Withdrawal practices were quite different between centres with a median interval from surgery to start of AED reduction of 12.5 months (95% confidence intervals 11.9–13.2) and time to complete discontinuation 28.8 months (95% confidence intervals 27.4–30.2), respectively. Ninety-five children had seizure recurrence during or after AED withdrawal (Boshuisen et al. 2012).

Data from neuropsychological assessments were available for 301 children and were analysed separately. Start of AED withdrawal, number of AEDs reduced, and complete AED withdrawal were associated with improved postoperative IQ scores and gain in IQ, independent of other determinants of cognitive outcome (Boshuisen et al. 2015).

**PROGNOSIS OF EPILEPSY**

The prognosis of epilepsy syndromes varies according to aetiology, associated manifestations, and patient age. Therefore, studies that do not specify specific populations are of limited value. They may only indicate overall prognosis assuming that referral patterns are not overly selective or biased.

However, a brief overview of some prognostic aspects of the epilepsies of children in general (the risk of recurrence after a first seizure, the risk of relapse after discontinuation of drug therapy, the problem of intractable epilepsy, the social and educational outcome of epilepsy, the risk of sudden death in adolescents and young adults) can provide a useful framework for studying the needs of the community, individuals and their families. Studies of global prognosis of childhood epilepsy reveal that certain factors (e.g. frequency of seizures, presence or absence of neurological or cognitive deficits, type of seizure, duration of seizures) have a strong correlation with
the outcome of epilepsy. These factors have predictive value, not only for unclassified cases of epilepsy but also for some well-defined syndromes.

A state-of-the-art workshop (Arts et al. 2013), focussed on data from cohort studies, trials and studies on treatment, current knowledge on outcome of childhood epilepsy in general and of specific types and syndromes. The workshop also identified areas of unknown knowledge and future research topics.

**RISK OF RECURRENCE AFTER A FIRST UNPROVOKED SEIZURE**

Recurrence rates after a first generalised tonic-clonic seizures vary between 25% and 54% (Annegers et al. 1986; Bouloche et al. 1989; Shinnar et al. 1990, 1996, 2000; Berg et al. 1998; Haut et al. 2007). Most occur within one year. These results suggest that treatment of a first seizure (First Seizure Trial Group 1993; Beghi 2007), is not indicated as half the children will remain seizure-free. Risk factors for recurrence include an neurodevelopmental delay, young age (<4 years), family history of epilepsy, and an abnormal EEG (Shinnar et al. 1994). The recurrence risk is 25% at 24 months after an idiopathic first seizure and a normal EEG, 34% when the EEG was abnormal but non-epileptiform, and 54% with epileptiform abnormalities. Early age at onset (<2 years) is strongly associated with medically resistant epilepsies primarily due to cases of epileptic encephalopathy. When these are excluded, the recurrence rate for infants is the same as for older children (Camfield et al. 1993).

These figures apply only to cases of isolated seizures or epilepsies. The risk of recurrence is much higher when neurological signs or intellectual disability are present. In a longitudinal study of 246 children, Sillanpää (1993) found that 5-year terminal remission after 35 years was 80% in idiopathic epilepsy, 69% in cryptogenic epilepsy, and only 56% in symptomatic cases. While 77% of patients with normal neurological and intellectual status attained a 5-year terminal remission, this decreased to 50% for patients with intellectual disabilities, 46% with cerebral palsy, and 29% when both intellectual disability and cerebral palsy were present. Even a minor neurological abnormality significantly decreased the probability of remission. However, in a large population of both children and adults with newly diagnosed epilepsy, Cockerell et al. (1997) found a 3-year remission rate of 86% and 5-year remission rate of 68% at 9-year follow-up.

In a study aimed at defining the prospects of newly diagnosed childhood epilepsy, assessing the dynamics of its course, identifying relevant variables and developing models to assess the individual prognosis, Arts et al. (2004) evaluated 453 children with newly diagnosed epilepsy followed for 5 years to define the course of newly diagnosed childhood epilepsy, assess its dynamics and identify relevant variables and developing models. Terminal remission at 5 years (TR5) was compared with terminal remission at 2 years (TR2) and with the longest remission during follow-up. Variables defined at intake and at 6 months of follow-up were analysed for prognostic power. Three-hundred and forty-five children (76%) had a TR5 more than 1 year, 290 (64%) more than 2 years and 65 (14%) had no seizures during the entire follow-up. Of 108 children (24%) with TR5 <1 year, 27 had intractable seizures at 5 years.

Medication was commenced in 388 children (86%). AEDs were withdrawn in 227 (59%). A TR5 more than 1 year was achieved by 46% on one AED, 19% on two AEDs, and 9% on all additional AED regimes. Almost 60% of the children treated with a second or additional AED regime had a TR5 more than 1 year. Variables predicting outcome at study onset were aetiology, history of febrile seizures and age. When onset and 6-month variables were combined, sex, aetiology, post-ictal signs, history of febrile seizures and terminal remission at 6 months were all significant. The course of the epilepsy was persistently favourable in 51%, persistently poor in 17%, improving in 25% and deteriorating in 6%. Intractability was, in part, only a temporary phenomenon. The outcome at 5 years in children with newly diagnosed epilepsy was favourable in 76% with 64% off medication. Almost a third of the children had a fluctuating course; improvement was clearly more common than deterioration.

To provide evidence as to whether different patterns of evolution of drug resistance and remission exist, Sillanpää and Schmidt (2006a) performed a prospective, long-term population-based study of 144 patients, followed on average for 37.0 years (SD 7.1, median 40.0, range 11–42) after a first seizure before the age of 16 years. Nearly half of childhood-onset epilepsy entered terminal remission without relapse, and one-fifth did so after relapse. One-third had a poor long-term outcome with persistent seizures after remission or without remission.

These studies are useful for understanding the natural history of the epilepsies, but the samples are relatively small. Larger subject pools are required to define different aetiologies. Relapse rates are also likely to vary considerably among populations with varied epilepsy aetiologies.

**RISK OF RELAPSE AFTER DISCONTINUATION OF TREATMENT**

The risk of relapse is relatively small in children who are seizure-free for 2 or 3 years on therapy (Bouma et al. 1987; Arts et al. 1988; Ehrhardt and Forsythe 1989; Aldenkamp et al. 1993; Shinnar et al. 1994). Figures vary between 12% and 42%, suggesting that discontinuation of therapy after 2 years is probably possible for most common seizure types. Dooley et al. (1996) found that the recurrence rate was no higher with discontinuation of treatment 1 year after the last seizure compared to 2 years, and Tennison et al. (1994) found no difference in recurrence rate between a 6-week and a 9-month weaning period. Similar results were obtained in a prospective study by the Medical Research Council (1991).
The long-term outcome for seizure relapse after planned discontinuation of AEDs in seizure-free patients was evaluated in the longitudinal population-based study of 148 patients from the onset of their epilepsy at average follow-up of 37 years (Sillanpää and Schmidt 2006b). AEDs were completely discontinued in 90 patients. Seizure relapse after AED discontinuation occurred in 33 (37%) at average follow-up of 32 years. Among eight of the 33 patients who restarted AEDs, two achieved 5-year terminal remission, but only 10–19 years after restarting treatment. The remaining six patients never achieved long remission, and two of six never entered a 5-year remission. Factors associated with failure to achieve remission were symptomatic aetiology and localisation-related epilepsy.

**DRUG-RESISTANT (INTRACTABLE) EPILEPSY**

Drug-resistant epilepsy is defined as epilepsy with uncontrolled seizures despite ‘relevant’ therapy (Juel-Jensen 1968). This definition is highly imprecise as the definition of adequate therapy is variably appreciated, and the level of control of epilepsy and the assessment of adverse effects are highly individualised. Some patients are inadequately treated rather than being drug resistant, and it is therefore essential to look for factors associated with apparent intractability such as an unrecognised neurological disorder, precipitating factors and treatment irregularities. Misdiagnosis of the epilepsy type results in the selection of an inappropriate drug – for example, ethosuximide for focal seizures, carbamazepine for myoclonic seizures – or failure to recognise that the seizures are not epileptic and caused by psychogenic or cardio-circulatory disturbances (Aicardi and Shorvon 1998). Differential diagnosis is discussed later in this chapter.

Even ‘true’ drug resistance falls along a continuum rather than being all-or-nothing. Partial control may be possible and beneficial, although optimal quality of life is best achieved by complete seizure control (Birbeck et al. 2002; Spencer et al. 2007).

The concept of ‘drug resistance’ cannot be defined in any one way. Individual studies use different definitions, creating difficulties for comparisons of results across studies. In a prospective cohort of 613 children in Connecticut with newly diagnosed epilepsy (1993–7), six different published definitions or indicators for intractability were applied and compared (Berg and Kelly 2006). All definitions were assessed at various times within the first 5 years after diagnosis, with the exact timing reflecting how their use in initial reports. Depending on the definition used, the epilepsy in 9–24% of children was considered drug resistant. All definitions were strongly associated with remission status at last follow-up and with longer-term outcome. The authors concluded that no single preferred definition of intractable epilepsy exists and that consideration should be given to whether a single or different definitions are required. We would add that ‘drug resistance’ should not be confounded with ‘prognosis’.

Approximately 20–30% of epilepsy is resistant to drug therapy. Intractable epilepsies include many ‘catastrophic epilepsies’ or ‘epileptic encephalopathies’, including the Lennox–Gastaut and Dravet syndromes, and cases of focal seizures that are usually lesional in origin. The molecular and cellular mechanisms underlying drug resistance are unknown (Sisodiya 2005; Remy and Beck 2006).

The natural evolution of focal non-idiopathic (structural) epilepsy is variable and it often difficult to decide how many trials of mono- and polytherapy should be considered. Clearly when other therapeutic options – especially resective surgery – are available and have a good prospect of success, medical therapy should probably not be prolonged for more than some months or even less with deterioration. However, drug regimens will be tried for much longer periods for epilepsy resistant to medical therapy and not amenable to surgery.

Predictors of drug resistance include infantile spasms, remote symptomatic epilepsy, a history of status epilepticus, neonatal seizures and microcephaly (Berg et al. 1996). To determine prospectively when in the course of epilepsy intractability becomes apparent, Berg et al. (2006) analysed the data from a prospective cohort of 613 children followed for a median of 9.7 years. Epilepsy syndromes were grouped into focal, idiopathic, catastrophic and other. Drug resistance was defined in both a stringent (two drugs failed, and one seizure/month, on average, for 18 months) and less rigorous way (failure of two drugs). Delayed intractability was defined as 3 or more years after epilepsy diagnosis. Eighty-three children (13.8%) met the stringent definition and 142 (23.2%) met the two-drug definition.

Intractability depended on syndrome (P<0.0001): 26 children (31.3%) meeting the stringent definition and 39 (27.5%) meeting the two-drug definition had delayed intractability. Intractability was delayed more often in focal than in catastrophic epilepsy (stringent: 46.2% versus 14.3%, P=0.003; two-drug: 40.3% versus 2.2%, P=0.0001). Early remission preceded delayed intractability in 65.4–74.3% of cases. After becoming intractable, 20.5% subsequently entered remission and 13.3% were seizure-free at last contact. These findings help explain why surgically treatable epilepsies may take 20 years or longer before referral to surgery.

To improve patient care and facilitate clinical research, the ILAE appointed a Task Force to formulate a consensus definition of drug-resistant epilepsy (Kwan et al. 2010). The aim was to provide a general scheme to categorise response to each therapeutic intervention, including a minimum dataset of knowledge about necessary intervention and a core definition of drug-resistant epilepsy. A set of essential criteria based on response to trials of antiepileptic drugs was employed. Issues related to frequency and severity of seizures were deliberately excluded from the definition as not critical to the concept of drug resistance and subject to individual interpretation. The Task Force also stated that complete seizure-freedom is the only relevant outcome consistently associated with improved
quality of life. ‘Duration of active epilepsy’ was also excluded, since it is more related to overall prognosis.

The number of AEDs was considered instrumental, primarily to avoid undue delays, which however were frequent, in identifying drug-resistant epilepsy and refer to an epilepsy specialist. Drug-resistant epilepsy was defined as failure of adequate trials of two tolerated, appropriately chosen and managed antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom.

We consider this definition to be a clinically meaningful consensus, underscoring the fact that early recognition of a given epilepsy as ‘difficult-to-treat’, rather than being a conclusion should be interpreted as the starting point for a multidisciplinary expertise. The definition is applicable to all types of epilepsies, either ‘benign’ or related to aetiologies favouring an increased seizure frequency.

**EDUCATIONAL, LEARNING AND BEHAVIOUR PROBLEMS**

Although the majority of children with epilepsy do not have learning difficulties or behavioural issues, one-fifth to one-third may be symptomatic from underlying CNS lesions (Sillanpää 1992, 2004; Beghi et al. 2006). Conversely, 20% of children with intellectual disability have epilepsy, and one-third also have cerebral palsy (Forsgren et al. 1990).

Various educational and behavioural difficulties may occur in children with epilepsy who are cognitively intact. The prevalence of psychiatric disorders is several times higher in children with epilepsy than in the general population (Freilinger et al. 2006; Austin and Caplan 2007), and emotional regulation disorders are common but often unrecognised (Plioplys 2003; Caplan et al. 2005; Reilly et al. 2015). The cause of these associations is unclear as they are not explained by differences in sex, age, presence of physical disability or low intelligence.

School underachievement is significantly more common in children with epilepsy (Seidenberg et al. 1986; Arts et al. 2004; Hermann and Seidenberg 2007). This is likely to be due in part to limited intellectual abilities in some patients. Bourgeois et al. (1983), Rodin et al. (1986) and Aldenkamp et al. (1990) have shown that some children with epileptic seizures may develop intellectual difficulties as a consequence of seizures, their treatment and socio-educational factors. However, many patients with epilepsy, even when well controlled were overqualified for their jobs (Olsson and Campenhausen 1992) suggesting low self-esteem or low parental expectations (Levin et al. 1988; Collins 1990).

Sillanpää (1990) showed that professional underachievement was also common in adult patients with epilepsy starting in childhood, even with a normal IQ. Loiseau et al. (1983) have shown that children with absence epilepsy have poorer social and professional achievement, than would be expected from their IQ scores or the benignity of their epilepsy. In contrast children with benign partial epilepsy have a completely normal prognosis. The reasons for such differences are poorly understood.

Considerable attention has been given to the contribution of subclinical EEG discharges to interference with learning or cognitive processes involving attention, concentration or specialised tasks (Arts et al. 1988; Kasteleijn-Nolst Trenité et al. 1988, 1990; Aldenkamp et al. 1992; Arzimanoglou et al. 2005; Deonna and Roulet-Perez 2005; Koop et al. 2005). However, important subclinical discharges may be, their relationship to all of the behavioural and learning difficulties of many children with epilepsy is complex. Feelings of inadequacy and specialised neuropsychological deficits correlate with aggressive behaviour, poorer school performance, fewer friends and fewer interests (Hermann 1982; Viberg et al. 1987; Fastenau 2011). Prospective studies, involving a large sample of children with newly diagnosed epilepsies and a long-term follow-up are lacking. Careful assessment and remedial help may be needed on an individual basis. In an overwhelming majority of children with epilepsy, regular schooling is possible, and special schools for patients with epilepsy are rarely – if ever – justified for patients without other neurodevelopmental problems.

**SOCIAL AND EDUCATIONAL OUTCOME**

The educational level of persons with epilepsy is much lower than the general population. In a long-term study of adults with childhood-onset epilepsy, Sillanpää (1992) found that approximately one-third of 176 patients received less than primary education and 37% only primary education. Only 18% went to secondary school and 9% graduated; 3% had a university degree. The proportion of patients with a driving licence (61%), of those married or having a stable relationship (65%), of those having children (49.5%) were all significantly lower compared to controls. The proportion who were unemployed (9.1%) was higher. Patients with active epilepsy did significantly less well than those who had been in remission for 5 years or more.

Another study from Finland (Koponen et al. 2007) explored social functioning and psychological well-being in a population-based cohort of epilepsy patients compared to matched controls identified through the National Registry of Social Insurance Institution. The age at onset of epilepsy was significantly associated with the level of further education, and the level of seizure control with employment status. Patients with epilepsy and a lower level of basic education had a significantly lower level of further education, employment, and fewer social relations. Some differences in psychological well-being were also seen in those who had passed a matriculation examination when compared to matched controls.

The most important conclusion of the study was that in young adults with well-controlled epilepsy social functioning and successful basic education is comparable to healthy peers. This suggests that social and educational support during the time of basic education may be crucial to favourable
intellectual, functional, and social development later in life. Both professional and informal support is needed in addition to conventional treatment of epilepsy.

All the above figures reflect, in part, the presence of complicating factors such as neurological impairment, learning difficulties and intellectual disability. However, even patients without complicating factors do less well than the general population in terms of professional and social adjustment (Loiseau et al. 1983). This is probably due, in part, to school absenteeism, low expectations from parents and teachers, rejection by peers, and practical problems (e.g. lack of driving licence). Many of these factors reflect prejudice and poor understanding by the public and the patients themselves about their condition. This situation could be improved by better awareness.

RISK OF DEATH IN YOUNG PEOPLE WITH EPILEPSY

Mortality rates are increased in people with epilepsy (Nilsson et al. 1997; Shackleton et al. 1999). A review of published series (Shackleton et al. 2002) showed that the mortality risk in patients with epilepsy is dependent on specific patient cohorts. Considerable unexplained variance remains among different source populations. Hence no uniform summary estimate for the elevated mortality is possible.

In a series devoted exclusively to childhood epilepsy, mortality during the first 10 years after onset was 5.7%, and another 2.9% died between 11 and 12 years after seizure onset (Kurokawa et al. 1982). Trevathan et al. (1997) reported that 4% of their epileptic population died before 11 years of age. An Australian study found a mortality rate of three per 1000 individuals, compared with 0.23 per 1000 in control children (Harvey et al. 1993c). Mortality was found to be higher in those epilepsies with onset before age 1 year in symptomatic epilepsy and infantile spasms than epilepsies with grand mal seizures.

Excess mortality is also present in population-based studies. In a review of the literature, Harvey et al. (1993c) found the mean estimate of death in epileptic children younger than 15 years was approximately five per 1000 children. Children with secondary epilepsy accounted for 94% of all deaths.

In a prospective community cohort of 613 children (Berg et al. 2004), symptomatic aetiology and epileptic encephalopathy were independently associated with mortality. The overall standardised mortality ratio for the cohort was 7.54. In children with symptomatic epilepsy, the standardised mortality ratio was 33.46 (95% confidence intervals, 18.53–60.43) and 0.43 (95% confidence intervals, 0.36–5.73) in non-symptomatic epilepsy. These results suggest that children with epilepsy have an increased risk of death and that most deaths occur in children with severe underlying conditions and are not directly related to the occurrence of seizures.

The overall mortality among patients of all ages is two to three times the general population (O’Donoghue and Sander 1997). Although the causes of death are quite variable, sudden unexpected death, accidents and suicide deserve special consideration.

 Suicide is one of the most important causes of increased mortality in persons with epilepsy. In a case–control study Nilsson et al. (2002) found a nine-fold increase in risk of suicide with mental illness and a ten-fold increase in relative risk with the use of antipsychotic drugs. The profile of the epilepsy patient who commits suicide that emerges from this study was an individual with early seizure onset, particularly during adolescence (but not necessarily severe epilepsy), psychiatric illness, and perhaps inadequate neurological follow-up.

Sudden unexpected death in epilepsy refers to sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death (Nashef et al. 1997). The cause of SUDEP is most likely heterogeneous with regard to both mechanisms and circumstances. A unified definition and classification (Nashef et al. 2012; Ryvlin et al. 2013) found that the most important risk factor is the occurrence and frequency of generalised tonic–clonic seizure (GTCS), which triggers the majority of witnessed episodes. Therefore, preventing SUDEP must minimise the risk of GTCS with optimal medical management and patient education. Another hypothetical strategy to prevent SUDEP is to reduce the risk of GTCS-induced postictal respiratory distress. This might be achieved by using a lattice pillow, providing nocturnal supervision, reinforcing interictal serotoninergic tone, and lowering opiate- or adenosine-induced postictal brainstem depression (Ryvlin et al. 2013). However, as recognised by the authors and by a recent Cochrane review (Maguire et al. 2016), very low-quality evidence of a preventive effect for nocturnal supervision against SUDEP is currently available. Further research is required to identify the effectiveness of other current interventions, for example seizure detection devices, safety pillows, SSRIs, early surgical evaluation, educational programmes, and opiate and adenosine antagonists.

SUDEP mainly occurs in adolescents and young adults and constitutes a significant cause of mortality in this age group. The rate is around one per 1000 patients per year (Nashef et al. 1995) so the issue clearly warrants continued investigation. A retrospective study from Australia (Opeskin et al. 2000) examined 15751 autopsy records covering a 6-year period; 357 cases had epilepsy, 50 of which (14%) were classified as SUDEPs. The SUDEP rate was approximately one per 3000 individuals with epilepsy per year. This study suggested the following positive associations: young age, tonic–clonic seizures, seizure frequency greater than ten per year, duration of epilepsy more than 10 years, intellectual disability, psychiatric disease and alcohol abuse. The role of factors such as AED compliance, psychotropic drug prescription and
recent unusually stressful life events was less clear. These observations support the hypothesis that seizures are the mechanism of many cases of SUDEP. The associations observed were largely in agreement with previous studies.

The mechanisms of sudden death in epilepsy are obscure. Asphyxia and cardiac dysrhythmias are likely factors. However, impressive apnoeic seizures with major cyanosis do not necessarily suggest a poor prognosis. Hewerton et al. (1994) reported a benign outcome in four of six infants and children with such events. Ryvlin et al. (2006b) discussed the pathophysiology and potential prevention of SUDEP. According to the authors, ictal arrhythmias may represent a more prevalent cause of SUDEP than previously recognised. There are no specific recommendations regarding the most appropriate therapeutic strategies to prevent SUDEP apart from the supervision at night of patients with refractory convulsive epilepsy (Langan et al. 2005).

The question of whether to discuss the risk of SUDEP, and when to discuss it, with patients with epilepsy is a major unresolved issue. Similar to other issues related to epilepsy treatment and care, the discussion of SUDEP should be considered on an individual basis (Shankar et al. 2017). It should take into account the wishes of the patient to discuss SUDEP and the possibility of specific protective measures (e.g. night surveillance for drug-resistant cases, arguments in favour of better compliance).

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Chapter 16  Epilepsy and Other Seizure Disorders


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Headache Disorders in Children

Kenneth J Mack

Primary Headache Disorders

Migraine
  Types of Migraine
  Evaluation and Diagnosis of Migraine
  Treatment and Prognosis of Migraine

Chronic Daily Headache Disorder
  Evaluation of Chronic Daily Headache
  Treatment and Prognosis of Chronic Daily Headache

Tension Type Headache

Trigeminal Autonomic Cephalalgias
  Cluster Headache
  Paroxysmal Hemicrania and SUNCT Syndrome
  Ice Pick Headaches

Secondary Causes of Headache

Cerebral Venous Sinus Thrombosis
  Pseudotumour Cerebri (Idiopathic Intracranial Hypertension)
  Headache in Chiari Malformations
  Trauma Related Headache
    Epidural Haematoma
    Subdural Haematoma
  Headache and Meningitis
    Bacterial Meningitis
    Viral Meningitis
  Headache and Brain Tumours
  Headache and Vascular Malformations
  Headache and Brain Abscess
  Headache and Hydrocephalus
Headache Disorders in Children

Kenneth J Mack

Headache is a common childhood complaint. Headaches can be divided into the primary headache disorders, such as migraine, and the secondary headache disorders, which are due to an underlying disorder.

PRIMARY HEADACHE DISORDERS

MIGRAINE

Migraines are severe, often bilateral, throbbing headaches frequently located in the temples or frontal head regions. Migraine occurs in 2–5% of preschool children, 10% of school-aged children and 20–30% of adolescent girls (Abu-Arafeh and Russell 1994; Aromaa et al. 1998). Approximately 20% of migraine patients experience their first attack when younger than 5 years of age (Bille 1997).

Symptoms of migraine vary with the age of the child. In preschool children, migraine often consists of episodes involving an ill, pale appearance, abdominal pain, vomiting and the need to sleep. Pain may be expressed by irritability, crying, rocking or seeking a dark room in which to sleep. Five to ten-year-old patients with migraine tend to experience bilateral frontal, temporal or retro-orbital headache with associated nausea, abdominal cramping, vomiting, photophobia, phonophobia and a need to sleep. Parents may describe these children as pale with dark circles under the eyes. Older children tend to present with a unilateral, temporal headache and the location and intensity of pain often change within or between episodes.

Migraine can occur with or without aura. Only 10–20% of children with migraine experience an aura, often for the first time after the age of 8 years. The aura usually precedes the headache by less than 60 minutes and lasts for 5–20 minutes. The aura may present without headache. Children often are unaware of or unable to describe their aura. The visual aura is the most common form in children, consisting of blurred vision, fortification spectra (zigzag lines), scotomata (field defects), scintillations, black dots, kaleidoscopic patterns of various colours, micropsia, macropsia (distortion of size) and metamorphopsia (‘Alice in Wonderland’ syndrome). Visual auras often are reported as moving or changing shapes; other auras include attention loss, confusion, amnesia, agitation, aphasia, ataxia, dizziness, vertigo, paresthesia or hemiparesis. Aura symptoms vary widely within and between episodes.

The headaches can last 60 minutes to 48 hours, but usually last less than 4 hours. Some young patients report short headaches lasting 10–20 minutes. The severity of childhood headache often is milder than adult migraines. The headache phase can be associated with cold extremities, nausea, anorexia, vomiting, diarrhea or constipation, dizziness, chills, excessive sweating, ataxia, numbness, photophobia, phonophobia, memory loss or confusion. Often the patient cannot concentrate or function effectively during or immediately after episodes. Relief typically is associated with sleep. After the headache phase, the patient may feel either elated and energised or more typically exhausted and lethargic. This stage of migraine may last from hours to days (Gladstein et al. 1993).

Migraine is associated with a variety of comorbid conditions. Psychiatric symptoms such as depression, panic episodes, anxiety disorders or phobia may be present. Epilepsy and migraine often occur within the same individual, although most patients with migraines do not have seizures. Migraineurs are more prone to motion sickness than patients without migraine. Intermittent vertigo is found frequently in patients with migraine. There is a higher cardiovascular reactivity to postural changes in patients with migraine and this may result in dizziness. Migraines are also associated with sleep disturbances and ice-cream headache in some patients (Raskin and Knittle 1976; Kuritzky et al. 1981; Schoenen et al. 1998; Dodick et al. 2003; Maizels and Burchette 2004; Pellock 2004).

Types of Migraine

Status migrainosus is a severe form of migraine in which the headache attack is continuous for longer than 72 hours. Patients usually have a pre-existing migraine history. In those who vomit, rehydration is often the necessary first step. One often effective treatment can be intravenous fluids, an antiemetic, and dihydroergotamine (DHE) (Linder 1994).

Familial hemiplegic migraine is an autosomal-dominant form of migraine with aura. Patients have a prolonged
hemiplegia that can be accompanied by numbness, aphasia and confusion. The hemiplegia may precede, accompany or follow the headache and symptoms may last from hours to days. The headache usually is contralateral to the hemiparesis. Some familial hemiplegic migraine is associated with cerebellar ataxia. Other types of severe familial hemiplegic migraine may present with coma, fever and meningismus. Some forms of familial hemiplegic migraine respond to acetazolamide or calcium channel blockers. Structural lesions, vasculitis, cerebellum. The occipital headache must have at least two of the following aura symptoms: dysarthria, vertigo, tinnitus, hyperacusia, diplopia, bi-field visual symptoms, ataxia, decreased level of consciousness or bilateral paresthesias. A history of typical migraine exists in many families. Some patients experience basilar migraine episodes intermingled with typical migraine episodes (Brenner et al. 2007).

**Basilar-type migraine** is a subtype of migraine with aura and is observed mostly in adolescent and young adult females. Headache pain may be located in the occipital area. Basilar-type migraine is characterised by disturbances in function believed to originate from the brainstem, occipital cortex and cerebellum. The occipital headache must have at least two of the following aura symptoms: dysarthria, vertigo, tinnitus, hyperacusia, diplopia, bi-field visual symptoms, ataxia, decreased level of consciousness or bilateral paresthesias. A history of typical migraine exists in many families. Some patients experience basilar migraine episodes intermingled with typical migraine episodes (Brenner et al. 2007).

**Benign paroxysmal vertigo of childhood** is a condition characterised by brief episodes of vertigo, disequilibrium and nausea, usually found in children aged 2–6 years. The patient may have nystagmus within but not between the episodes. The child does not have hearing loss, tinnitus or loss of consciousness. Symptoms usually last only a few minutes. These children often develop a more common form of migraine as they mature. Brain magnetic resonance imaging (MRI) can be obtained to exclude posterior fossa abnormalities, especially if abnormalities in the neurological examination are found between episodes (Abu-Arafeh and Russell 1995).

**Acute confusional migraine** is characterised by transient episodes of amnesia, acute confusion, agitation, lethargy and dysphasia. This form of migraine is often precipitated by minor head trauma. The child may have a receptive or expressive aphasia, and the confusional state may either precede or follow the headache. Some children also experience recurrent episodes of confusion. The patient usually recovers within hours. The child may not have a history of headache but usually develops typical migraine episodes when older. It is important to exclude hypoglycaemia, intoxications, encephalitis, structural lesions and seizures (Shaabat 1996).

Migraine-associated **cyclic vomiting syndrome** is characterised by recurrent periods of intense vomiting separated by symptom-free intervals. Many patients with cyclic vomiting have regular or cyclic patterns of illness. Symptoms usually have a rapid onset at night or in the early morning and last 6–48 hours. Associated symptoms include abdominal pain, nausea, retching, anorexia, pallor, lethargy, photophobia, phonophobia and headache. The headache may not appear until the child is older. Migraine-associated cyclic vomiting syndrome usually begins when the patient is a toddler and resolves in adolescence or early adulthood; it rarely begins in adulthood. More females than males are affected by cyclic vomiting. Usually a family history of migraines in the parents or siblings is present. These children often experience severe fluid and electrolyte disturbances that require intravenous fluid therapy. Migraine-associated cyclic vomiting syndrome is a diagnosis of exclusion. Other causes of cyclic vomiting include gastrointestinal disorders (malrotation), neoplasms, urinary tract disorders, metabolic, endocrine and mitochondrial disorders (Andersen et al. 1997; Rashed et al. 1999).

In **abdominal migraine**, the patient may suffer from recurrent bouts of generalised abdominal pain with nausea and vomiting, but often with no headache present. The episodes are often relieved by sleep and later the child awakens feeling better. Abdominal migraine may alternate with typical migraine and can lead to typical migraine as the child matures. These children respond to migraine prophylactic medication (Dignan et al. 2001; Russell et al. 2002).

**Paroxysmal torticollis of infancy** is an uncommon disorder characterised by repeated episodes of head tilting associated with nausea, vomiting and headache. Episodes usually occur in infants and may last from minutes to days. Posterior fossa abnormalities should be considered in the differential diagnosis. As with hemiplegic migraine, recent data has linked these symptoms to mutations in the CACNA1A gene in some patients (Abu-Arafeh and Russell 1995; Drigo et al. 2000; Giffen et al. 2002).

**Acephaligic migraine of childhood** (migraine sine hemiconia) is characterised by a migraine aura without headache, usually visual auras and a female predominance. A family history of migraine is frequent.

**Migraine aura** occurs in about one-third of adult and adolescent patients and can consist of blurred vision, fortification spectra (zigzag lines), scotomata (field defects), scintillations, black dots, kaleidoscopic patterns of various colours, micropsia, macropsia (distortion of size) and metamorphopsia (‘Alice in Wonderland’ syndrome). Visual auras often are reported as moving or changing shapes; other auras include attention loss, confusion, amnesia, agitation, aphasia, ataxia, dizziness, vertigo, paresthesia or hemiparesis. Aura symptoms vary widely within and between episodes. In contrast, **retinal migraine** is an uncommon condition where there are repeated episodes of monocular (as opposed to hemifield or binocular) visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache (Lendvai et al. 1999).

**Ophthalmoplegic migraine** is a poorly understood inflammatory disorder, rather than a primary headache disorder. Patients present with an ophthalmoplegia, typically a unilateral IIIrd nerve palsy and headache. During an attack, MRI studies may demonstrate inflammation of the third cranial nerve,
although the aetiiology of the inflammation is rarely defined. Episodes may last for days and can be recurrent (Brenner et al. 2007).

Evaluation and Diagnosis of Migraine

No specific diagnostic tests for migraine exist and the diagnosis is made through the history, physical examination and clinical judgment. The child with migraine should have a normal general physical examination and a normal detailed neurological examination. Only a small percentage of headache patients require further laboratory and radiologic studies. An imaging study should be considered in patients with a history of seizures, recent head trauma, significant change in the headache, or evidence of focal neurological deficits or papilloedema upon physical examination. No absolute rules exist in the evaluation of the headache patient; the decision to perform a neuroimaging study ultimately is based on clinical judgment. Electroencephalography (EEG) is not useful in the routine evaluation of headache patients. It should be considered in patients with an atypical migraine aura, episodic loss of consciousness or symptoms suggestive of a seizure disorder. Lumbar puncture is indicated if meningitis, encephalitis, subarachnoid haemorrhage or high-low pressure syndromes are considered. Patients in whom elevated intracranial pressure is suggested or with focal neurological deficits should undergo a neuroimaging study prior to a lumbar puncture (Lewis et al. 2002).

Treatment and Prognosis of Migraine

The treatment of migraine headaches should emphasise identification of environmental trigger factors, pain control at the time of the headache and preventive medication. The treatment of children with mild, infrequent episodes consists primarily of rest, trigger avoidance and analgesics. The patient and parents benefit from a simple explanation of the headache pain and reassurance that it is not caused by a brain tumour or other life-threatening condition. A regular bedtime, regular meal schedules and avoidance of overloading the child’s schedule with activities are important. Helping the child recognise migraine triggers is helpful but often difficult. It is important that the patient has realistic expectations; identifying and avoiding triggers reduces the frequency of migraine headache but does not eliminate headaches.

Psychological triggers include stress, anxiety, worry, depression and bereavement (Anttila et al. 2004). Emphasising to the patient and family that migraine is not an imagined or psychological illness is important. Stress is not the sole cause of the headaches, although it makes migraines more difficult to manage. Physiological triggers include fever or illness, missing a meal, fatigue and sleep deprivation. Environmental triggers of migraine include fluorescent light, bright light, flickering light, fatigue, barometric pressure changes, high altitude, strong odours, computer screens or rapid temperature changes. Some patients report that complex visual patterns like stripes, checks or zigzag lines may trigger migraines. Physical exertion can trigger childhood migraine. Some migraineurs report that they are more likely to get a headache after participating in sports or being extremely active. Minor head trauma (e.g. being hit in the head with a ball, falling on one’s head) also may result in a migraine attack. Travel or motion may cause migraine, particularly in young children (Jan 1998).

At the time of the headache, advise the child to lie down in a cool, dark, quiet room and fall asleep. Sleep is the most potent antimigraine treatment. Some patients find that ice or pressure on the affected area of pain can alleviate pain temporarily. Nonsteroidal anti-inflammatory agents are effective if taken at an appropriate dosage during the aura or early headache phase. Gastric stasis occurs in migraine patients and causes delay in absorption of oral medications. Occasionally, carbonated beverages may improve absorption. Nonpharmacological treatment modalities such as self-relaxation, biofeedback and self-hypnosis may be reasonable alternatives to pharmacological treatment in managing childhood migraine, particularly in adolescents (Lewis 2004).

Prophylactic or preventive medications are taken on a daily basis to reduce the frequency or severity of headaches and associated symptoms. A good response to prophylactic medications is often considered a 50% reduction in the frequency or severity of episodes. Consider the use of prophylactic drugs for children with frequent (>2 per week), prolonged and disabling migraine episodes that do not adequately respond to other treatments. Often, several weeks are necessary before therapeutic gains are observed with prophylactic medications. Possible preventive medications include amitriptyline, propranolol, gabapentin, valproate, topiramate, flunarizine, verapamil and riboflavin (Hershey et al. 2000; Silberstein et al. 2012). Unfortunately, there is limited high-quality evidence for the best preventive treatment of migraine in childhood. In part, it is difficult to demonstrate efficacy of a single approach because of the traditionally high placebo response rates in children, which approach 50–70% in some studies. This was evidenced in a recent high-quality randomised controlled trial study that compared placebo to topiramate to amitriptyline. In that study the placebo response rate approached 60% and topiramate and amitriptyline failed to exceed that rate of success (Powers et al. 2017). Still, the best available evidence supports the use topiramate and cognitive behavioural therapy in the treatment of migraine.

Migraines may change in frequency as children move into adulthood. In one of the few longitudinal studies of childhood migraine patients, children with migraine were followed for 40 years (Bille 1997). The average age at onset of the migraines was 6 years. During puberty or young adulthood, 62% of the children were migraine-free for at least 2 years; approximately 33% of these children regained regular episodes after an average of six migraine-free years and a surprising 60% of the original 73 children still had migraines after 30 years; 22% of the participants never had a migraine-free year. Of those patients who became parents, 52% have at least one child in their present or previous families who developed recurrent migrainous headache.
CHRONIC DAILY HEADACHE DISORDER

Chronic daily headache is a disorder where the diagnosis is based on the presence of headache for greater than or equal to 15 headache days in 1 month, over a period of three consecutive months, and with no underlying organic pathology. The headaches last for more than 4 hours per day. This headache disorder tends to affect adolescents and adults, but can occur before puberty. It can occur in up to 4% of young women and up to 2% of young men, with similar prevalence rates seen in studies from Asia, Europe and the United States (Kavuk et al. 2003).

Silberstein and others (1996) have defined four different categories of chronic daily headache based upon symptoms. These include transformed or chronic migraine, chronic tension type headache, new daily persistent headache and hemicrania continua. Many adolescents with chronic daily headache have a past history of episodic migraine. The transformation to a chronic migraine may occur over a period of weeks to months, or it may occur abruptly over a matter of hours (Mack 2004). Approximately a quarter of adolescents with chronic daily headache will have no significant past headache history and an infection such as mononucleosis or a minor head injury may incite a new, daily persistent headache (Mack 2004). A smaller number of patients will have a history of tension type headaches prior to their chronic daily headache.

Most commonly, the youngster with chronic daily headache will complain of at least two types of headaches. Prominent are severe intermittent headaches that are migraine-like. They tend to be pancephalic or frontal in location. The severe headaches will be described as throbbing, severe, crushing, knife-like or hatchet-like. They are often associated with nausea during the most severe times and the patient will frequently have photophobia, phonophobia and osmophobia. For this more severe headache pain, sleep will sometimes help, but they will still have persistent headache when they awaken. The frequency of these severe headaches will vary with the individual. The severe episodes typically occur multiple times a week.

In addition to these severe intermittent headaches, the patient with chronic daily headache will often complain of a continuous headache that is present 24 hours a day, 7 days a week. This continuous headache may wax and wane in severity, often being worse either in the morning or at the end of the school day. The characteristics of the all-the-time headache pain are similar to the episodes of severe headaches, only much less intense. Some patients may also describe this all-the-time headache as having features of a tension type headache, with the pain being band-like or crushing rather than throbbing.

Headache is not the only symptom in chronic daily headache; it is really a multi-symptom complex. Sleep is disrupted in at least two-thirds of the patients who have chronic daily headache. Typically, the headache syndrome will not resolve until the sleep is improved (Dodick et al. 2003).

Many chronic daily headache patients also complain of dizziness which is associated with feeling weak, unsteady and with blurry, or loss of, vision. This is often positional and may involve syncope or near syncope several minutes after standing. There is typically no vertigo, except during severe headache episodes. The dizziness is particularly prominent in the morning. A difference in blood pressure or pulse rate between sitting and standing may be noted and the patient often experiences mild symptoms of this dizziness if stood up for several minutes in the office. One may see either a significant tachycardia with standing (postural orthostatic tachycardia syndrome) and/or a decrease in the systolic blood pressure with standing (Raskin and Knittle 1976; Johnson et al. 2010).

Mood problems and anxiety also frequently coexist with chronic daily headache. The mood problems may precede or follow the onset of the headache. Both the symptoms of headache and mood need to be addressed. If there are significant problems with mood and anxiety, it is difficult to control the headaches until these symptoms are improved. Other frequent comorbid symptoms include non-specific abdominal pain, back pain, neck pain and diffuse muscle and joint pain and often no additional organic aetiology is found to explain these additional pain symptoms. There are important environmental factors that play a role in these headaches. There is an interesting seasonal variability in the degree of chronic daily headache symptoms. Most patients will do better in the summertime and frequently have a worsening of their headaches at the start of the school year and school absence can be a significant problem (Sartory et al. 1998).

In addition to the preventive treatments listed above for migraine, there are other therapies that should be considered in chronic migraine. Onabotulinumtoxin type A has been shown in randomised controlled trials in adults to be effective in reducing headache levels and migraine days. There are retrospective studies in adolescents that have shown similar effectiveness to what is seen in adult populations (Ahmed et al. 2010). The Cefaly antimigraine device is a neurostimulatory device that is placed on the forehead, similar to a tiara, and used for 20 minutes each day to decrease the headache burden (Schoenen et al. 2013). It seems to be best tolerated by patients without allodynia. In some patients with chronic post-traumatic headaches or neuralgia, selective trigger point injections with a local anaesthetic can be useful in decreasing pain.

The next generation of medications that will be developed for migraine and chronic migraine will affect CGRP, a neurotransmitter associated with pain (Schuster and Rapoport 2016). There are several approaches being developed in parallel by at least five pharmaceutical companies and the end products will have the potential for either abortive or preventive use.

Evaluation of Chronic Daily Headache

Neuroimaging studies will be normal in the overwhelming majority of chronic daily headache patients. Occasionally in these patients, white matter abnormalities, arachnoid cysts or pineal cysts will be seen that are generally believed to be of no clinical significance in relation to the chronic daily
headache. If a patient has had a significant history of head or neck trauma, particularly at the onset of the chronic daily headache, then magnetic resonance angiogram (MRA) of the neck should also be considered to rule out a possible carotid dissection. When pseudotumour cerebri is a strong consideration, then an magnetic resonance venography (MRV) should also be considered since sinus thrombosis can cause elevated intracranial pressure. Serum studies to consider include evaluation of the thyroid, sedimentation rate and antinuclear antibodies (ANA). Many patients will transition from a headache-free period or episodic migraines to chronic migraines during an infection so consideration should be given to serology for Epstein–Barr virus, West Nile virus and other viral or bacterial infections (Lewis et al. 2002; Mack and Gladstein 2008).

**Treatment and Prognosis of Chronic Daily Headache**

Chronic daily headache is difficult to control and it typically takes weeks to months to effect a change in headache control. The cornerstones of therapy are education, preventive medications and attention to environmental trigger factors. It is difficult for many families to comprehend that the head pain can persist for such a long time, that there are no abnormalities showing up on diagnostic testing and that the medications they are prescribed are not immediately effective. It is thus useful to spend adequate time with the patient and family discussing the role of medications, when not to use pain relievers, the role of non-medication approaches (such as biofeedback or physical therapy), and what the family should expect in the short and long term. After 1 month of an effective therapy, a reasonable expectation would be to have less frequent severe headache episodes, and a decrease in the intensity of the all-the-time, 24/7 headache. It is rare to see complete resolution of the headaches after a short period of time. Once a trend toward improvement is seen, the dose of medication is adjusted for optimal control of the headaches, and the patient is continued on the preventive for at least 6 months of good (but rarely complete) symptom control. It is not unusual to make frequent adjustments in management initially, and it may take months before matching up the right preventive medication or the right therapeutic approach with the individual patient (Galli et al. 2004).

Preventive medications are traditionally used in episodic migraines to reduce the frequency of the migraine headaches. However, in chronic daily headache, a reasonable therapeutic goal would be to make the severe intermittent headaches less frequent, and to make the all-the-time headache less intense. The most published experience of preventives in chronic migraine or chronic daily headache is the use of medicines that work on the serotonergic system or the anticonvulsants. Unfortunately, there have been few prospective randomised controlled studies in children to give us guidance as to what is the most effective or safe medication to use in chronic daily headache (Lewis et al. 2004).

Studies in adults and children have shown that tricyclic antidepressants, such as amitriptyline, are helpful in chronic daily headache. Consideration needs to be given to following electrocardiogram (ECG) changes, as this drug may prolong the QT interval. Weight gain is a significant concern in adolescents with these medicines, and it affects some children more than others. Amitriptyline can also be helpful for sleep onset. Other tricyclics, such as nortriptyline or protriptyline, may cause less sedation (Hershey et al. 2000).

Other serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs) have also shown to be effective in some adults with chronic headache. The SSRIs seem to be less effective than the tricyclics for pain control, although they are more helpful in children for their positive effects on mood. In select patients, the use of an SSRI can be very useful (Saper et al. 1994).

Studies in headache patients have shown anticonvulsants are also useful. Valproate, topiramate and gabapentin have been used. Choice of rational pharmacotherapy to treat the patient’s other problems is ideal. Antidepressants can address underlying mood disorders as well as sleep problems. Beta-blockers can make depression worse; however, they may be helpful for patients with a postural orthostatic tachycardia syndrome. Calcium channel blockers are useful for patients who also have hypertension, but cause constipation and orthostatic hypotension. If the patient needs to lose weight, topiramate is a good choice, although this may result in cognitive clouding. The use of botulinum toxin shows promise as well (Mack and Gladstein 2008).

**Hemicrania continua** is a rare headache syndrome, occurring in approximately one percent of chronic daily headache patients. It is a persistent unilateral headache pain. The pain may be characterised by a stabbing sensation and may be associated with autonomic changes. It is important to recognise this entity since these patients may respond to daily doses of indomethacin to ameliorate this condition.

Pain control at the time of the headache is a very difficult problem for patients. Analgesics that are typically effective for episodic migraine headaches are not very effective for chronic migraine or chronic daily headaches. Most patients report that pain relievers are not effective for the all-the-time, 24/7 headache. It is reasonable to discourage patients from trying to use analgesics to treat the all-the-time headache, since this may result in analgesic overuse and a potential analgesic rebound headache. Combating rebound from those substances is part of the treatment. Medications implicated in this overuse syndrome include most over the counter analgesics and decongestants, opioids, butalbital, isometheptene, benzodiazepines, ergotamine and triptans.

In contrast, for the more severe intermittent headache episodes with migrainous qualities, analgesics should be considered. Approaches can include the use of migraine pain relievers such as triptans, indomethacin or other nonsteroidal anti-inflammatory agents. Compounds that contain caffeine, barbiturates, opiates, or that have a high potential for rebound
should be limited or avoided. Patients typically find that when the preventive medication starts working, then the pain analgesics will become more effective also. Additional treatment strategies include dihydroergotamine, intravenous valproate or steroids. Non-pharmacological approaches to the headaches are also very important. Because of the chronic nature of the pain, some patients will benefit with a consultation with a psychologist to at least be introduced to the techniques of relaxation therapy and biofeedback. Many of the patients have been ill for months to years and have become physically ‘deconditioned’. Starting a reconditioning exercise programme is very important. Patients should be encouraged to start slowly. For the most severely affected patients, begin with 10 minutes of aerobic exercise a day and then increase the time by 10% a week. There is limited data looking at the outcome of chronic daily headache in children. The average time by 10% a week. There is limited data looking at the outcome of chronic daily headache in children. The average duration in childhood is unknown, but it is not unusual to see children who have chronic daily headaches persisting for months to years.

TENSION TYPE HEADACHE

Migraine and tension type headache are the most common types of headache in children and adolescents. The actual prevalence of tension type headache in children is uncertain because it varies with the defining criteria, but studies have reported anywhere from 0.9–73% of affected children. Age at onset has been reported in studies as between 5 and 12 years. The headaches tend to occur more frequently in females during adolescence and genetics plays less of a role in this disorder than in migraine. The pathophysiology is incompletely understood but may involve trigeminal activation. The headaches are characterised by a variable intensity, bilateral, dull, pressure pain with occasional associated phonophobia that lasts from minutes to days. There are three subtypes defined by the International Headache Society classification. Episodic tension type headache may be infrequent (less than one day per month) or frequent (1–14 days per month) and chronic tension type headache occurs 15 or more days per month. Diagnosis is based on the clinical history and a normal neurological examination including vital signs and funduscopic examination. The differential diagnosis is broad and includes a variety of organic disorders such as infection, malformation, bleed and systemic disorders. The value of neuroimaging in the presence of a typical history and normal neurological examination is low, but is recommended if there is vomiting, a history of trauma, seizure or an abnormality on examination. Tension type headache or medication overuse headache may progress into chronic daily headache. Treatment of episodic tension type headache involves reassurance, stress reduction, psychological and cognitive behavioural therapies and appropriate use of an acute analgesic medication, such as a nonsteroidal anti-inflammatory drug. Treatment of chronic tension type headache may involve the above in addition to a prophylactic medication such as an antidepressant (Anttila 2006; ICHD 2013).

TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal autonomic cephalalgias refer to a group of headaches that are characterised by repetitive, brief episodes of severe unilateral pain associated with ipsilateral autonomic features including rhinorrhea, nasal congestion, lacrimation and conjunctival injection. They include cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome. They each differ in the duration, frequency and rhythmicity of episodes. All are more common in adults and have rarely been reported in children.

CLUSTER HEADACHE

Cluster headache is the most common trigeminal autonomic cephalgia. The prevalence in adults is less than 1% and has a male predominance. The prevalence in childhood and adolescence has been estimated to be 0.1%. Studies have noted childhood onset after the age of 5 years. The pathophysiology is not completely understood but theories involve hypothalamic activation and neurogenic inflammation. Symptoms include several bouts per day, generally with circadian rhythmicity, lasting weeks of severe unilateral orbital, supraorbital or temporal head pain lasting 15 minutes to 3 hours with associated unilateral autonomic features and associated restlessness (Majumdar et al. 2009). Children may experience thrashing about or emotional outbursts secondary to the severe pain. There are episodic (most common) and chronic forms and a familial predisposition. Diagnosis is made clinically but a head computed tomography (CT) or MRI should be performed to exclude an underlying brain lesion. The differential diagnosis includes other trigeminal autonomic cephalalgias and an underlying brain lesion. Treatment involves preventive medications such as verapamil and acute treatment such as oxygen, triptans or steroids. The patient should be cautioned against triggers, such as smoke and alcohol.

PAROXYSMAL HEMICRANIA AND SUNCT SYNDROME

Paroxysmal hemicrania is rare in children. Episodes are shorter (minutes), more frequent and less severe than in cluster headaches. These headaches are exceptionally responsive to treatment with indomethacin.

Short-lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing (SUNCT) syndrome is also rare in children. Episodes are very short in duration (seconds to minutes), triggered by touching the face or chewing, have limited associated autonomic features and occur up to hundreds of times per day.
ICE PICK HEADACHES

Ice pick headaches are a benign primary headache disorder characterised by sudden ice pick-like pains. These pains may last for seconds to minutes, typically occur at different parts of the child’s head, and are often seen in patients prone to migraines. They are fairly infrequent and most often do not require treatment. There are case reports of these headaches responding to indomethacin.

SECONDARY CAUSES OF HEADACHE

CEREBRAL VENOUS SINUS THROMBOSIS

Cerebral venous sinus thrombosis is a serious disorder that frequently presents with headache. Diagnosis and treatment may be delayed secondary to its varied clinical presentation unless it is considered and investigated as a potential aetiology (see Chapter 15). The annual incidence in a multicentre Canadian registry of children 18 years of age and younger was 0.67 per 100,000. In children there is no female predominance as is seen in young adults (deVeber et al. 2001). Risk factors and presenting symptoms are related to age. Neonates are most commonly affected and risk factors include hypoxic encephalopathy or other perinatal complications, infection and dehydration. In children, risk factors include acute or chronic systemic illnesses, anaemia, infection (especially of the head and neck), prothrombotic states and dehydration.

The clinical presentation in neonates includes seizures and diffuse neurological signs. In children it may include headache, changes in cognitive status, papilloedema, emesis and focal neurological signs. Headache is the most frequent symptom. The headache onset is generally acute to subacute, and the intensity moderate to severe. The pain is typically continuous and localised, exacerbated by recumbency and Valsalva manoeuvres, and unrelieved by analgesics. Neuroimaging should be performed, and include head MRI and MRV because head CT may be normal in about 30% of patients. This will demonstrate an absence of blood flow in the cerebral veins. Treatment involves antithrombotic therapy utilising intravenous heparin followed by warfarin for several months. In cases of extensive thrombosis, thrombolytic therapy and mechanical thrombectomy may be considered. Outcomes vary from resolution with normal neurological function in about half to neurological sequelae (motor, cognitive, speech) and death (deVeber et al. 2001; Agostoni 2004; Sebire et al. 2005).

PSEUDOTUMOUR CEREBRI

(Idiopathic Intracranial Hypertension)

Idiopathic intracranial hypertension is a syndrome of increased intracranial pressure with normal neuroimaging studies, normal cerebrospinal fluid (CSF) composition and elevated CSF pressure (Friedman and Jacobson 2002). In adults it is frequently associated with obese females of childbearing age. In children, however, it is less frequently associated with obesity and female sex. Symptoms include those of elevated intracranial pressure: headache, nausea, vomiting and visual disturbances. Headache is the most common presenting symptom and may be daily, pulsatile and exacerbated by supine positioning. Infants with headache may present more subtly with only changes in sleep and behaviour. Neurological examination may demonstrate cranial nerve palsies, especially abducens palsy and papilloedema. Papilloedema is considered a characteristic finding; however, it may not be seen in infants because of their unfused sutures, and is an inconsistent finding in children and adolescents. Associated factors to inquire about in the history include the use of acne medications, antibiotics, vitamin A intake and oral contraceptives (Genizi et al. 2007).

Diagnosis is one of exclusion and is based upon the 1985 Modified Dandy Criteria: an awake and alert patient, signs/symptoms of increased intracranial pressure, absence of localising findings on neurological examination except for abducens nerve palsy, normal CSF findings except for increased pressure (>250mm water), absence of ventricular system anomaly on imaging studies and lack of other cause identified (Friedman et al. 2013). Neuroimaging should be performed to evaluate for mass lesions causing obstructive hydrocephalus or dural venous sinus thrombosis. A lumbar puncture should be performed after a mass lesion has been ruled out by imaging to evaluate for increased intracranial pressure. Treatment in children may involve acetazolamide, corticosteroids, serial lumbar punctures, lumbar peritoneal shunting or optic nerve sheath fenestration. Patients should be referred to an ophthalmologist for an examination including visual field testing and continued visual monitoring as visual loss is a complication. Outcome is generally favourable (Soler et al. 1998).

HEADACHE IN CHIARI MALFORMATIONS

Headaches may be a presenting symptom of a Chiari I malformation (see Chapter 6). There are four types of Chiari malformations but because the other malformations are generally evident at birth, a type I malformation is the most likely to be discovered in childhood. Type I Chiari malformation refers to the downward displacement of the cerebellar tonsils through the foramen magnum. It may be associated with obstructive hydrocephalus and syringomyelia. The incidence is unknown because many patients are asymptomatic and remain undiagnosed. Headache is a common presenting symptom and may
be exacerbated by Valsalva manoeuvre or physical exertion. The head pain may be located in various areas and may occur multiple times daily and last seconds to minutes. Presenting complaints may also include neck pain, sensory, motor or gait impairments or oropharyngeal dysfunction. Neurological examination findings may include scoliosis, abnormal deep tendon reflexes and cranial nerve deficits. Diagnostic testing should include brain MRI, including the posterior fossa, craniovertebral junction and upper cervical levels. Surgical treatment for children presenting with headache is generally controversial but may include suboccipital craniectomy and cervical laminectomy (Weinberg et al. 1998; Greenlee et al. 2002).

TRAUMA RELATED HEADACHE

Epidural Haematoma
Trauma is a common cause of injury and loss of consciousness in children and may be associated with a potentially life-threatening epidural haematoma. In an epidural haematoma there is haemorrhage, commonly from the middle meningeal artery, and accumulation of blood between the dura mater and the skull. This blood initially strips the dura away from the skull, causing pain and eventually exerts mass effect on the brain which can lead to herniation and death. Thus it is important to quickly recognise the symptoms and efficiently manage children with epidural haematoma who may present with headache.

Risk factors include falls, motor vehicle accidents, direct head injuries and skull fractures. Patients may experience an asymptomatic, lucid interval following the initial injury then develop headache associated with nausea, vomiting and altered cognitive status. Late and ominous findings indicating compression of the brain stem include focal neurological findings, pupillary changes, bradycardia, hypertension and respiratory depression. Clinical presentation varies with age. In newborn infants, epidural haematomas may complicate delivery and may present with seizures, hypotonia and pallor. Older children may present with headache, nausea and vomiting several hours following a head injury associated with loss of consciousness. Diagnosis is via head CT which demonstrates a convex, hyperdense mass that generally does not cross suture lines. Treatment depends on the physical examination and head CT findings. Surgical management involves haematoma evacuation, and non-surgical management involves serial imaging and observation. Outcome can be favourable with prompt diagnosis and surgical management (Heyman et al. 2005).

Subdural Haematoma
Subdural haematomas result from venous tearing and haemorrhage into the potential space located between the dura and arachnoid. Risk factors include falls, motor vehicle accidents and trauma. Infants are predisposed to subdural haematomas because they have relatively larger heads, subdural spaces and weaker neck muscles compared with older patients.

Other predisposing factors include a history significant for a haemorrhagic disorder, an arachnoid cyst or shunted hydrocephalus. Onset of symptoms may be delayed days to weeks due to the relatively lower pressure venous system. Infants may present with a bulging fontanelle and irritability. Young children may present with seizures, increasing head circumference, hypotonia and focal neurological signs. Non-accidental trauma should be considered in the differential diagnosis of a young child with a subdural haematoma. Associated factors may include retinal haemorrhages, bruises, fractures or a previous history of abuse. Older children may present with altered cognitive status, headache and vomiting. Late findings indicating compression of the brainstem include focal neurological findings, pupillary changes, bradycardia, hypertension and respiratory depression.

Diagnosis of subdural haematoma is by head CT which demonstrates a concave, hyperdense mass which crosses suture lines. Additional studies to consider in a child with a subdural haematoma include a blood count, coagulation studies, fundoscopy and skeletal survey. Treatment depends on the physical examination and head CT findings and outcome varies. Surgical management involves haematoma evacuation or shunt placement and non-surgical management may involve serial imaging, observation and intracranial pressure monitoring (Jayawant et al. 1998; Vinchon et al. 2003).

HEADACHE AND MENINGITIS

Meningitis refers to inflammation of the tissues surrounding the brain and spinal cord. Aetiology includes bacteria, viruses, fungi and parasites (see Chapter 11). Headache is a frequent early symptom.

Bacterial Meningitis
Bacterial meningitis is life-threatening, and the most common causative agents depend on patient factors such as age, immunisation status and presence of underlying predisposing factors. Risk factors include living in an endemic area, immunocompromise, lack of immunisation against Haemophilus influenzae type b or Streptococcus pneumoniae, recent infection (especially upper respiratory, ear or sinus), head trauma, ventricular shunts or cochlear implants.

The most common aetiological organisms vary with age and location. In neonates, group B streptococci, Listeria monocytogenes and Gram-negative enteric bacilli (Escherichia coli, Klebsiella, Enterobacter, Salmonella) are common agents. Worldwide, S. pneumoniae, N. meningitidis and H. influenzae type b are common causes of bacterial meningitis in young children and S. pneumoniae and N. meningitidis are common in older children. Clinical features and examination findings may include headache, fever, neck stiffness, photophobia, altered cognitive status, nausea, vomiting, irritability, seizures, cranial nerve palsies, petechiae and purpura.

Evaluation should include CSF cell count, differential, glucose, protein, culture and serum blood count, differential,
glucose, culture and possibly neuroimaging. Imaging should be performed prior to lumbar puncture if there is concern for increased intracranial pressure that may result in herniation during the lumbar puncture. Disease progression may be fulminant so empirical antibiotic therapy may need to precede lumbar puncture and imaging. However, a blood culture should be obtained initially.

CSF findings include pleocytosis with neutrophil predominance, elevated protein, decreased glucose and a positive Gram stain. A positive CSF culture is diagnostic as is a positive blood culture in the setting of CSF pleocytosis. Complications include shock, increased intracranial pressure, seizures, subdural effusions and abscesses. Treatment should be initiated empirically while awaiting culture results and then altered if necessary when a specific organism is identified. Recommendations for empirical therapy of bacterial meningitis by the Infectious Disease Society of America include vancomycin plus a third-generation cephalosporin for children older than 1 month. Adjunctive dexamethasone use to decrease the inflammatory response is recommended in infants and children with *H. influenzae* type b meningitis and should be given prior to the initiation of antimicrobials and continued for 2–4 days. Outcomes vary but persistent neurological sequelae are not uncommon following bacterial meningitis (Tunkel et al. 2004; Chavez-Bueno and McCracken 2005).

**Viral Meningitis**

Viral meningitis is more common than bacterial meningitis in children. It is also known as aseptic meningitis and refers to an inflammation of the meninges without evidence of bacteria in the CSF. Various infectious agents such as enterovirus, herpesvirus, arbovirus, influenza and rabies may be responsible but non-polio enteroviruses are the most common cause of viral encephalitis in the United States. Worldwide, there is a diverse range of pathogens that may cause viral encephalitis. Arboviruses have a global distribution but are found primarily in tropical regions. West Nile virus is an arbovirus that is found in North America. Paediatric West Nile virus may present with a febrile illness and may include meningitis, encephalitis and a poliomyelitis-like illness (Gubler 1996).

Clinical presentation may include fever, headache, nausea, vomiting, photophobia and change in cognitive status. Young children may present with fever, irritability, rash or seizures. Common aetiologies include group B coxsackieviruses and echoviruses. Evaluation should include lumbar puncture and CSF analysis to rule out a bacterial aetiology. Pleocytosis is seen and may be neutrophilic initially and then become more lymphocytic. Treatment is supportive and prognosis is generally favourable (Rorabaugh et al. 1993; Sejvar 2006).

**HEADACHE AND BRAIN TUMOURS**

Headache may be the presenting symptom of a brain tumour in children. Brain tumours (see Chapter 14) are the most common solid organ cancer and second to leukaemia as the most common overall cancer in children. Presenting signs and symptoms vary with the age of the child and with the location of the tumour but frequently include headache (especially nocturnal or early morning), nausea, vomiting, unsteadiness, seizures, behaviour changes, papilloedema and focal neurological deficits. The majority of childhood brain tumours are located infratentorially. Location of the tumour determines clinical presentation. For example, brainstem gliomas may present with cranial neuropathies due to their compression of exiting cranial nerves. Cerebellar astrocytomas and medulloblastomas may present with ataxia due to their location in the cerebellum as well as symptoms of increased intracranial pressure because of fourth ventricular compression. Ependymomas tend to arise from the floor of the fourth ventricle, which is near the vomiting centre, and may present with nausea, vomiting or obstructive hydrocephalus. Supratentorial midline tumours such as craniopharyngiomas and gliomas may present with visual deficits, eye movement abnormalities, neuroendocrine dysfunction, behavioural and appetite changes due to their location near the optic chiasm and pituitary gland (Pollack 1999).

Headache is a common complaint in children and deciding which children to image can be challenging. Recent studies have investigated clinical predictors of underlying brain tumour in children presenting with headache and found that a headache that causes nocturnal awakening or is present upon awakening, as well as a negative family history of migraine, were predictors of underlying brain tumour. Additional predictors include headache duration of less than 6 months, vomiting, seizures, confusion and an abnormal neurological examination. Diagnosis is via neuroimaging with and without the use of contrast, MRI is generally preferred over CT because the posterior fossa is better visualised. Treatment depends on the histological diagnosis, tumour location and age of the child but may involve surgery, chemotherapy, radiation and other modalities such as anticovulsant medications or bone marrow or stem cell reconstitution. Prognosis varies with tumour type (Medina et al. 1997; Wilne et al. 2006).

**HEADACHE AND VASCULAR MALFORMATIONS**

Cerebral vascular malformations include venous angiomas, arteriovenous malformations, capillary telangiectasias and cavernous malformations (see Chapter 15). Venous angiomas are the most common and are usually benign. Clinical presentation may include headache as well as dizziness, incoordination, seizures, motor or sensory deficits. Diagnosis is via MRI and treatment is conservative. Capillary telangiectasias are usually asymptomatic and may be found incidentally on neuroimaging studies (McLaughlin et al. 1998).

Cavernous malformations and arteriovenous malformations are more likely to cause neurological symptoms. Cavernous malformations may be sporadic or familial. Clinical presentation may include headache, haemorrhage, seizure or focal
neurological sign. Diagnosis is via MRI and treatment depends on symptoms and location but may involve surgical resection, or stereotactic radiosurgery (Labauge et al. 1998).

Arteriovenous malformations involve a loss of the normal vascular organisation. They consist of abnormal collections of dilated arteries and veins in the brain parenchyma. The most common presenting sign is haemorrhage but additional presentations include headache, seizures and neurological deficits. Haemorrhagic strokes are relatively common in children and may be due to an underlying arteriovenous malformation. Diagnosis is via neuroimaging, including CT angiography, which provides vascular detail, or MRI/MRA which provide visualisation of surrounding structures. Angiography is the criterion standard, however, because it allows for visualisation of the lesion and is useful in the assessment of haemorrhage risk. Treatment depends on many factors and may include surgical resection, radiosurgery or embolisation (Friedlander 2007).

HEADACHE AND BRAIN ABSCESS

Brain abscesses are generally uncommon in children but may develop in children with predisposing factors. Studies have identified congenital heart disease, otitis media, sinus or intracranial infections, intracranial hardware, skull fractures, intracranial surgery and immunosuppression (organ transplantation, chemotherapy, HIV) as predisposing factors for brain abscess development. Pathogenesis involves the invasion of micro-organisms (bacteria, fungi, parasites) into the brain parenchyma and can result from direct extension, hematogenous spread or penetrating trauma. Infants being treated for meningitis may present with a bulging fontanelle and increased head circumference. Older children may present with more obvious signs including vomiting, fever, headache, photophobia, cognitive status changes, seizure and focal neurological signs such as hemiparesis or visual field deficits. Early diagnosis and treatment leads to improved outcome. A brain abscess should be considered in a child with a history of congenital heart disease, immunosuppression, recent neurosurgical procedure or ear or sinus infection presenting with new onset headache, seizure or focal neurological sign. Neuroimaging with contrast should be performed and will demonstrate an enhancing rim around an area of decreased attenuation. Treatment generally involves monitoring with frequent brain imaging, several weeks of antibiotics and possible surgical intervention. Adverse outcomes may include hydrocephalus, seizures, developmental delay, neurological deficits or death (Goodkin et al. 2004).

HEADACHE AND HYDROCEPHALUS

Hydrocephalus is due to the accumulation of CSF secondary to an imbalance in its production and re-absorption (see Chapter 7). This may result from increased CSF production, decreased absorption or obstruction to flow, which is the most common cause. The resultant increased pressure results in dilatation of the ventricular system, affects its lining and the surrounding white matter. Congenital hydrocephalus may be a result of intrauterine infection, toxoplasmosis, or central nervous system (CNS) tumour or malformation. Acquired hydrocephalus may be the result of CNS infection, haemorrhage or tumour causing ventricular obstruction. Signs and symptoms include an excessive increase in head circumference, headache (especially morning), nausea, vomiting and changes in vital signs, level of consciousness and papilloedema. Acute hydrocephalus presents more obviously than chronic hydrocephalus, as the system has time to adjust to the changes. Diagnosis can be made by neuroimaging, including cranial ultrasound in infants or head CT or MRI. Treatment depends on the underlying cause but may involve CSF drainage and shunt placement. Complications of shunts include mechanical malfunction and infection. Headache is a frequent complaint in patients with shunts and should raise the suspicion for shunt malfunction or infection. Prognosis depends on cause, time to treatment and complications but may include seizures and developmental delay. Prognosis in untreated hydrocephalus is poor and may include death (Kahle et al. 2016).

REFERENCES


Sleep Disorders

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Paroxysmal Disorders of Sleep
- Night Terrors and Nightmares
- Somnambulism (Sleep Walking)
- Hypnagogic Phenomena
- Rapid Eye Movement Sleep Behaviour Disorder
- Abnormal Movements in Sleep

Sleep Apnoea Syndromes
- Obstructive Sleep Apnoea Syndrome
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- Other Syndromes Featuring Sleep Apnoea

Hypersomnia and Insomnia Syndromes
- Narcolepsy-Cataplexy
- Other Syndromes with Hypersomnia
- Kleine–Levin Syndrome
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Sleep Disorders

Patricia Franco

The mechanisms and role of sleep are still mysterious. In children sleep has different neurophysiological and clinical features from that in adults, while maturational changes with age in the development of clinical and electroencephalogram (EEG) sleep stages have been extensively studied (Dan and Boyd 2006).

Childhood sleep disorders are one of the most prevalent complaints in paediatrics (Halbower and Marcus 2003). Childhood obstructive sleep apnoea, for example, has a prevalence of 1–4%. Some, such as narcolepsy, are often not recognised and raise considerable diagnostic problems. However, most disturbances of sleep in children are transient, benign and require only counselling and reassurance. A few common and/or important disorders are discussed in this chapter.

PAROXYSMAL DISORDERS OF SLEEP

NIGHT TERRORS AND NIGHTMARES

Night terrors usually occur between the ages of 18 months and 5 years (Guilleminault 1987a) and are associated with partial arousal from deep slow sleep (Stages III–IV). They supervene mainly during the first hours of sleep, with the child starting to scream and usually sitting up, looking terrified and although appearing to be awake does not recognise his or her parents and cannot be consoled. An episode lasts a few minutes before the child goes back to sleep and keeps no memory of the event. Night terrors may occur every night for periods then disappear. They may persist to age 8 years in 50% of children and decrease during adolescence (DiMario and Emery 1987; Laberge 2000). Nightmares may appear similar but take place during rapid eye movement (REM) sleep, at the end of the night when REM sleep is predominant. Both night terrors and nightmares are benign conditions and require only reassurance.

SOMNAMBULISM (SLEEP WALKING)

Somnambulism is frequent in older children. It is the consequence of incomplete arousal that permits some semi-purposeful activity without clear consciousness or memory of the event. Episodes are usually brief, with the child engaging in a simple activity such as going to the bathroom. Somnambulism may be associated with somniloquy and is characterised neurophysiologically by an incomplete arousal from slow sleep (Pedley 1983); hereditary factors may play a role in genesis. Night terrors and sleepwalking occur together in more than 50% of affected children and share the same genetic predisposition (DiMario and Emery 1987; Laberge 2000). They are grouped together under the term ‘non-REM parasomnias’.

HYPNAGOGIC PHENOMENA

These are brief episodes of auditory or visual hallucinations or distortions of perception, especially auditory or proprioceptive, that occur in the transition between wakefulness and sleep, most commonly on going to sleep. They may be a part of the narcolepsy tetrad (see below) but are more commonly a normal phenomenon.

RAPID EYE MOVEMENT SLEEP BEHAVIOUR DISORDER

Unconscious violent behaviour may arise from REM sleep in adolescents and adults but this syndrome is rare in childhood (Trajanovic et al. 2004).

ABNORMAL MOVEMENTS IN SLEEP

Restless legs syndrome can occur in children and adolescents (Kotagal and Silber 2004). It is characterised by an irresistible urge to move the limbs, usually accompanied by a peculiar discomfort in the lower limbs. It may cause difficulties in initiating or maintaining sleep and daytime sleepiness; a family history of the syndrome is frequently reported. Walters et al. (1994) reported it to be dominantly inherited in children with typical features of urge to move, paraesthesiae, motor restlessness and periodic limb movements (nocturnal
myoclonus). The syndrome may be associated with iron deficiency and affected children may be misdiagnosed as hyperactive or irritable, while the syndrome may be one cause of the so-called ‘growing pains’.

**Periodic movements in sleep** may be associated with restless legs syndrome and are more or less rhythmical, sometimes recognised only by pain in the legs on awakening (Martinez and Guilleminault 2004), while links with attention-deficit–hyperactivity disorder, narcolepsy and other sleep disorders are frequent (Picchietti and Walters 1999). Treatment with the dopamine agonist pramipexol or with gabapentin or the benzodiazepines can be useful.

Other involuntary movements of sleep in children include *myoclonic jerks on falling asleep* (Oswald 1959), *nocturnal myoclonus* that may be more or less rhythmical, *jactatio capitis nocturna* and nocturnal jerks sometimes associated with hyperekplexia (see also Chapter 19).

**Benign neonatal sleep myoclonus** is a well-defined and easily diagnosed condition, even though it is often mistaken for epileptic seizures or even status epilepticus. Rhythmic jerks of the limbs may be generalised or localised, occurring in brief or more prolonged bursts that can be repeated for hours, with the trunk and face remaining unaffected and jerks immediately ceasing on awakening (Resnick et al. 1986; Di Capua et al. 1993). Induction of the myoclonus by shaking the crib is a useful diagnostic manoeuvre (Alfonso et al. 1995): the myoclonus usually disappears in a few weeks but can persist up to several months. Physiological myoclonus should be differentiated from pathological myoclonus in newborn infants, which is not sleep-related, may involve the face and trunk and is associated with EEG abnormalities (Scher 1985; Alfonso et al. 1993).

**Nocturnal paroxysmal dystonia** (Lugaresi et al. 1986) is characterised by sleep-related seizures with choreoathetoid, dystonic and ballistic movements occurring every night in adult patients. Similar situations occur occasionally in children, with the symptomatology similar to that of some frontal lobe seizures; the disease often responds well to carbamazepine. Two subtypes are observed, short repeated episodes lasting only seconds to minutes and long-lasting episodes. It is currently recognised as a form of frontal lobe epilepsy that may be familial (Chapter 16).

### SLEEP APNOEA SYNDROMES

Several syndromes are characterised by the occurrence of abnormally frequent or prolonged episodes of apnoea during sleep (see Table 18.1). Normally, REM sleep is characterised by irregular breathing. Sleep apnoeas are a disabling problem because of their interference with sleep (sleep fragmentation and/or intermittent hypoxemia) which could induce growth impairment, school difficulties as well as learning and behavioural problems (Nixon and Brouillette 2005).

Episodes of apnoea that occur during sleep may be of three types (Guilleminault 1987b):

1. **Obstructive apnoea** is the unsuccessful maintenance of an airflow in spite of respiratory effort,
2. **Central apnoea** is the arrest of respiration because it fails to be initiated by the respiratory centres and
3. **Fixed apnoea** combines both mechanisms.

### OBSTRUCTIVE SLEEP APNOEA SYNDROME

Obstructive sleep apnea (OSAS) in children is characterised by recurrent events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal ventilation and sleep patterns (American Thoracic Society 1995). The incidence of OSAS is estimated to be from 2–4% whereas habitual snoring is more common and estimated to occur in 6–9% of school-aged children (Lumeng 2008). It occurs in children of all ages including neonates. OSAS is frequently diagnosed in children without neurological disorders between the ages of 2 and 6 years in association with adenotonsillar hypertrophy. Children with craniofacial anomalies and/or neurological disorders, stockage diseases such as mucopolysaccharidoses affecting upper-airway configuration and collapsibility during sleep may present OSAS at any time from early infancy through childhood. OSAS may be more common in children with a family history of the syndrome, infants with gastrooesophageal reflux, children of African-American race, children who are obese, born preterm or with chronic upper and lower respiratory tract diseases (Redline 1999; Raynes-Greenows 2012). Clinical features of OSAS can be divided into nocturnal signs such as loud snoring, laboured or paradoxical breathing, movement arousals, neck extension during sleep, secondary enuresis and daytime symptoms such as morning headaches, slow rate of growth, excessive daytime sleepiness, hyperactivity or aggressive behaviour; however, clinical criteria are insufficient for diagnosis (Marcus 2012a). Both clinical and polysomnographic features are required for the diagnosis of OSAS in children (International Classification of Sleep Disorders-3 [ICSD-3]). Children with OSAS may demonstrate several breathing patterns during sleep from obstructive apnea to obstructive hypoventilation, which consists of long periods of persistent partial upper airway obstruction associated with hypercarbia and/or arterial oxygen desaturation. Some children may manifest a pattern of upper airway respiratory syndrome (UARS) similar to that seen in adults, including snoring without identifiable airflow obstruction: an increased frequency of night terrors and somnambulism may be observed in these children (Guilleminault 2003). In children upper airway obstruction occurs predominantly during REM sleep, with complications frequent and possibly severe. In early childhood OSAS can cause growth failure, with cognitive and behavioural
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Complications common and which may include developmental delay, poor school performance, attention-deficit–hyperactivity disorder and aggressive behaviour. Cardiovascular complications include pulmonary hypertension, cor pulmonale and systemic hypertension while severe complications may result including cor pulmonale, failure to thrive and permanent neurological damage (Oren et al. 1987). Adenotonsillectomy is the most common treatment for pediatric obstructive sleep apnea and the first line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors (Guilleminault et al. 1986; Marcus et al. 1995; Nixon and Brouillette 2005; Marcus 2012). Residual obstruction

Table 18.1 Main causes of apnoea in infants and children

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*Gastrointestinal reflux remains a debated cause of apnoea.

1Exclusion diagnosis.

2 Apnoea, pallor, cyanosis, impression of imminent death. About half the cases are due to known disorders (respiratory, digestive, neurological or cardiac); the remaining cases are idiopathic and may be related to the sudden infant death syndrome and to sudden unexpected death in epilepsy patients (SUDEP) (see Chapter 16).
is not rare (30–70%), especially in children with additional risk factors such as obesity, craniofacial anomalies, severe OSAS and those older than 6 years (Bhattacharjee 2010). Weight management is indicated for obese children while medications including nasal steroids or montelukast in short therapy could be helpful (Brouillette 2001; Goldbart 2012): exposure to environmental tobacco smoke and other pollutants should be avoided while referral to an orthodontist for rapid maxillary expansion is recommended in individuals affected by residual OSAS (Pirelli 2004). Continuous or bilevel positive airway pressure can be used successfully in children and adolescents, even in young infants (Marcus 2012) and should be considered a palliative rather than curative therapy. Other surgical procedures such as nasal septoplasty and/or maxillofacial surgery are performed, only in selected children. Tracheostomy is rarely indicated except in patients affected by severe, life-threatening obstructive sleep apnea.

**CONGENITAL CENTRAL ALVEOLAR HYPOVENTILATION SYNDROME**

Congenital central alveolar hypoventilation syndrome (CCAHs), also known as ‘Ondine’s curse’, is a rare syndrome that occurs considerably less frequently than obstructive sleep apnoea syndrome. It is characterised by the depression of central ventilatory drive during quiet sleep and resulting in central apnoeas during sleep that are rapidly lethal if untreated. Trang et al. (2005) reported on 70 patients from France and found an overall fatality rate of 38%, with 43 patients surviving at a mean age of 9 years at the time of the study and 49 of 50 who lived beyond 1 year of age receiving night-time ventilation. Additional problems may include swallowing difficulties while abnormalities of the brainstem auditory evoked potentials have been found in patients with congenital or idiopathic CCAHS (Beckerman et al. 1986). A history of hydramnios is present in some patients (Alvord and Shaw 1982) and Hirschsprung disease (Commare et al. 1993) is probably the most common syndrome associated with episodes of apnoea. Boltshauser et al. (1987) and Magaudda et al. (1987) have reviewed these syndromes which include Joubert syndrome, Mohr syndrome and Dandy–Walker syndrome (Bordarier and Aicardi 1990). Magaudda et al. (1988) described a syndrome of familial, fixed, congenital encephalopathy with an undifferentiated sleep–waking EEG cycle, excessive startles and continuous periodic breathing. Episodes of ‘microsleep’ during wakefulness occur especially in patients with nocturnal insomnia (Tassinari 1976), can be mistaken for epileptic absences and may have the same unpleasant or dangerous consequences for the patients.

**HYPERSOMNIA AND INSOMNIA SYNDROMES**

**NARCOLEPSY-CATAPLEXY**

Narcolepsy consists of episodes of irresistible sleep occurring during daytime, most often during monotonous activity. The episodes, which last usually 10–20 minutes, appear on a background of more or less continuous sleepiness in most patients. Hypersomnia in narcolepsy is usually associated with one or more of the other elements of the tetrad of symptoms: cataplexy, hypnagogic hallucinations and sleep paralysis – but these do not necessarily occur together. Cataplexy is a sudden loss of muscle tone, precipitated by laughter or excitement: it results in the patient falling to the ground without losing consciousness and should be distinguished from epilepsy (Macleod et al. 2005), hyperekplexia, Niemann–Pick C disease and sudden falls that occur in patients with the Coffin–Lowry syndrome. The full tetrad occurs in only 10% of adult patients with many children presenting with behaviour problems or learning difficulties, both consequences of sleepiness and efforts to stay awake (Winter et al. 1996). Narcolepsy is a rare disease with an incidence of 0.03% in adult and pediatric population (Ohayon 2002; Partinen 2012). However, many adults with narcolepsy retrospectively admit to having
had the condition since childhood: about 80% of individuals have their onset before 20 years of age and up to 30% before age 15, with the earliest recorded onset in a 9-month-old child (Peeyon 2000). Two types of narcolepsy are currently recognised in the ICSD-3 (American Academy of Sleep Medicine 2014). Type 1 narcolepsy, based upon actual or presumed hypocretin deficiency, includes either cataplexy or a reduction in measured cerebrospinal fluid (CSF) hypocretin-1 levels. The deficit in hypocretin-1 (also called orexin) peptides released from the dorso-lateral hypothalamic neurons (Peyron et al. 2000; Thannickal et al. 2000) is probably secondary to an autoimmune destruction of hypocretin cells (Aran et al. 2009; Cvetkovic-Lopes et al. 2010). Type 2 narcolepsy is associated with normal CSF hypocretin-1 levels (if a lumbar puncture is performed) and based upon polysomnographic evidence, including a mean sleep latency shorter than or equal to 8 minutes plus at least two sleep onset rapid eye movement periods during multiple sleep latency tests and night polysomnography.

Ninety-eight per cent of narcolepsy–cataplexy patients belong to the human leukocyte antigen (HLA)-DR2 groups, especially DQB1-0602 (Kramer et al. 1987; Mignot 2001), although an extremely small number of patients exist that do not belong to these HLA groups (Confavreux et al. 1988). The gene(s) for narcolepsy may act through an autoimmune mechanism resulting in loss of orexin/hypocretin neurons when the patient is exposed to environmental stress such as infections or H1N1 vaccines (Orenalla 1994; Dauvilliers et al. 2007; Aran 2009; Hallmayer et al. 2009; Cvetkovic-Lopes 2010; Han 2011; Dauvilliers 2013). Indeed, there was a five-fold increase in incidence of narcolepsy in paediatric and adult population post H1N1 vaccination (Dauvilliers 2013). This relationship is present only in idiopathic cases and does not hold for narcolepsy due to acquired brain injury (Aldrich and Naylor 1989) that can rarely be observed with hypersomnia or with pontomedullary lesions (D’Cruz et al. 1994). Such lesions most commonly induce coma or permanent hypopernasia or sleepiness and the typical tetrad of narcolepsy–cataplexy is barely complete. Narcolepsy proper refers to the brief episodes of sleep that occur three to five times daily on average, with half the patients easy to awake during an attack and most children feeling unrefreshed afterwards, contrary to narcoleptic adults.

Cataplexy is defined as more than one episode of generally brief (<2 minutes), usually bilaterally, symmetrical sudden loss of muscle tone with retained consciousness (ICSD-3). The episodes are precipitated by strong emotions, usually positive, with almost all patients reporting some episodes precipitated by emotions associated with laughter. The finding of transient reversible loss of deep tendon reflexes during an attack, while rarely observed, is a strong diagnostic finding. In children (and rarely adults) cataplexy may present close to disease onset as facial (or generalised) hypotonia with droopy eyelids, mouth opening and protruded tongue or gait unsteadiness, which are not clearly related to emotion (Plazzi 2011). Facial and masticatory movements may occur. In children, anticipation of reward is a common precipitant.

Hypnagogic hallucinations and sleep paralysis are less common, respectively found in 40% and 30% of patients. The latter consists of generalised hypotonia with inability to move during the transition between sleep and wakefulness, with partial paralysis with inability to move any one body part more common and nocturnal insomnia, also a frequent complaint of narcoleptic patients. In young children day naps are often long (20–120 minutes) and often unrefreshing.

Episodes of amnesic automatism simulating epilepsy occur in 8% of patients (Aldrich 1990; Schenck and Mahowald 1992).

Sleep paralysis, cataplexy and hypnagogic hallucinations appear to reflect the fact that motor manifestations of REM sleep, whose immediate or rapid onset after falling asleep characterises narcolepsy, may also occur in slight chronologic dissociation from the behavioural component of sleep in narcoleptic individuals. Hypocretin is not only involved in sleep regulation but has also been implicated in a number of behaviour and neuroendocrine actions including modulation of feeding behaviour and energy balance (Baumann and Bassetti 2005). Accordingly, body weight or body mass index is frequently increased in patients with narcolepsy. Obesity has been reported in 30% of adults with narcolepsy (Schulz 2000) and is also a frequent coexisting feature in childhood narcolepsy. It may occur in at least 50% of all children with narcolepsy, especially the youngest ones (Inocente 2013) with increasing weight manifested relatively early in the course of the disease (Aran 2010). The high incidence of precocious puberty, obesity and central hypothyroidism in children could reflect broadly-based hypothalamic abnormalities (Poli 2013).

The course of narcolepsy is lifelong and often psychologically distressing (Inocente 2013, 2014). A good regimen of sleep is an essential component of therapy and includes a regular schedule of night sleep, the avoidance of long naps and provision of short periods of day rest. Treatment of narcolepsy with modafinil (Bastuji and Jouvet 1988) is effective to alleviate excessive daytime sleepiness. Methylphenidate and amphetamines may help some patients but their action is often transitory. Antidepressants such as the selective serotonin reuptake inhibitors (SSRI) or imipramine have a beneficial effect on cataplexy, with sodium oxybate acting as well on cataplexy frequency as on excessive daytime sleepiness and dyssomnia (Mamelak et al. 2001; Xyrem International Study Group 2005). New therapies such as the inverse agonist of the histamine H3 receptor appear promising (Dauvilliers 2013). Making the correct diagnosis (Stores 2006), offering simple reassurance that the disorder is not a psychiatric one, multidisciplinary follow-up and help with academics are of great importance. Isolated cataplexy has been reported with pontomedullary lesions (D’Cruz et al. 1994) in patients with Coffin–Lowry syndrome (Stephenson et al. 2005) and in patients with Niemann–Pick C disease and with Norrie syndrome (Chapter 17), in which it may account for the atonic episodes previously reported (Vossler et al. 1996).
OTHER SYNDROMES WITH HYPERSOMNIA

Hypersomnia is encountered in patients with sleep fragmentation, especially children with the obstructive sleep apnoea syndrome or the increased airway resistance syndrome: however sleep deprivation, especially in adolescents is probably the most common causes of diurnal hypersomnia, with depression and neurotic states frequent factors in adolescent patients.

Recurrent hypersomnia is occasionally caused by lesions of the third ventricle or brainstem such as tumours or sequelae of encephalitis, trauma or vascular accidents (Plazzi et al. 1996; Autret et al. 2001). It should also be kept in mind that hypersomnia could be a form of Munchausen by proxy by repetitive administration of sedatives.

KLEINE–LEVIN SYNDROME

Originally described in the 1930s, Kleine–Levin syndrome has received attention in paediatrics and child psychiatry only in recent years. It occurs mostly in adolescent boys (population prevalence unknown), and presents with the combination of intense hunger or specific craving for certain foods, increased need for sleep (somnolence and withdrawal or fugue-like states may be difficult to distinguish from each other) and a variety of emotional/behavioural/neuropsychiatric problems.

This symptom constellation appears abruptly and is present for a few days to a few weeks, whereafter symptoms subside. Weeks to months later a new episode occurs and follows a similar pattern, albeit quite often of more limited duration. New episodes can occur for a period of one to several years. Gradually, however, relapses tend to occur less often and the episodes become shorter and shorter.

Hypothalamic dysfunction may account for the symptomatology because: (1) the appetite and sleep symptoms implicate hypothalamic systems; (2) the syndrome occurs mostly during adolescence; (3) it affects mostly boys and the episodic nature could be seen as a counterpart to variable behaviour in connection with onset of menarche in girls; and (4) some EEG findings are compatible with hypothalamic dysfunction (Arnulf et al. 2015).

The work-up should include a neuropsychiatric assessment. If the history and symptoms are typical there is no need for further work-up but in case of doubt neurological and laboratory tests to exclude other neurological disorders and metabolic problems may be essential, while a urine and/or blood screen for narcotics and other drugs might also be appropriate for some patients. The EEG sometimes shows mild to moderate increase of low-frequency activity and there may be subtle signs of damage to the CSF blood–brain barrier.

Management need often consist only of assessment and a proper diagnosis. In severe cases affecting school attendance over long periods, a trial of stimulants might be indicated. In most cases, however, information given to the affected child/adolescent and to his/her parents and teachers will suffice.

Because of similarities between Kleine–Levin syndrome and certain mood disorders, lithium and carbamazepine may be prescribed. Responses to treatment have often been limited. This disorder needs to be differentiated from cyclic reoccurrence of sleepiness during the premenstrual period in adolescent girls that may be controlled with birth control pills.

Long-term outcome is good, although a year or two of school work may be wasted and most affected individuals do well by early adult life. The behaviour problems encountered are extremely variable and are often associated with some degree of somnolence and clouded consciousness.

All sorts of psychiatric diagnoses may be discussed before a correct diagnosis is established. These may range from depression or manic depression to schizophrenia and drug abuse. Encephalitis is commonly suspected if the family seeks help during the first episode. The episodic nature of the disorder might not be evident until three or more episodes have occurred. There is also commonly partial or total amnesia for the episodes.

INSOMNIA

Many young children, about 30% before the age of 5 years, have periods when they have difficulty going to sleep or staying asleep. It is usual when parents stay with the child until she or he falls asleep and this is a physiological event that should be managed with parents.

The phenomenon occurs less commonly in school-age children in whom it is often related to anxiety, especially based on school problems or emotional difficulties. Quality and quantity of sleep are negatively related to the hours spent in front of TV, computers, internet and mobile phones, while difficulties in getting to sleep are also common in children with attention-deficit–hyperactivity disorder (Chapter 30) and in children with learning difficulties.

Certain drugs such as phenobarbitone and lamotrigine are an often unrecognised cause of sleep disturbances in, toddlers or children with epilepsy while sometimes, a true depressive state is responsible. In a significant proportion of patients no cause is found and the prognosis is variable, with individuals affected in adolescence and adulthood.

In many children with neurodevelopmental disabilities such as autism spectrum disorders (Chapter 29), Angelman syndrome, Smith-Magenis syndrome (Chapter 5), severely involved cerebral palsy (Chapter 8) and blindness, the circadian rhythms are considerably disturbed, which often produces severe family life disruption. Melatonin may be a potent treatment for such individuals (Jan and Freeman 2004; Phillips and Appleton 2004).

For most patients no drug therapy is indicated. The use of hypnotics such as nitrazepam or chloral hydrate is rarely considered, when severe daily fatigue results from insomnia. Nocturnal awakening in young children, followed by resumption of sleep in the small hours of the morning, is a fairly common and benign behaviour that requires no more than reassurance. Seizures are a rare cause of insomnia responsible for excessive daytime somnolence. In some patients the seizures are limited to awakening associated with paroxysmal EEG bursts.
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Radiological Findings in Basal Ganglia Disease
The basal ganglia form what Gowers and Wilson called the ‘dark basement of the brain’. Dysfunction of the basal ganglia classically results in abnormalities of movement, and this will be the main focus of this chapter. However, many disorders that involve the basal ganglia also affect other parts of the nervous system. For example, diseases that were once thought to be caused only by dysfunction of the basal ganglia, such as Parkinson disease and Huntington disease, have been found to have diffuse abnormalities not only in the brain, but also in the peripheral and autonomic nervous systems (Obeso et al. 2014).

Movement disorders have always interested neurologists, but the emergence of movement disorders as a subspeciality discipline in neurology is a recent development. The Movement Disorders Society was formed in 1985, and in 1986 the Movement Disorders Journal was first published. The first paediatric textbook devoted to Movement Disorders, by Emilio Fernández-Alvarez and Jean Aicardi, appeared in 2001. In previous editions of Diseases of the Nervous System in Childhood, movement disorders were not treated as a distinct topic, but appeared in multiple places in the text.

At the time of writing, advances in genetics are producing profound changes in the approach to children with movement disorders. Previously, diagnosis was almost entirely reliant on the clinical prowess of the examiner, and required an encyclopaedic knowledge of a vast but scattered literature. Now, genetics is giving us answers that are at times surprising, and not uncommonly humbling. One example is the finding that paroxysmal kinesigenic dyskinesia is caused by mutations in the proline rich transmembrane protein 2 gene (Wang et al. 2011), a totally unexpected outcome in a condition that had long been assumed to be a channelopathy. It has also become clear that different mutations in the same gene can produce very different clinical pictures (genetic pleiotropy). A short list of genes that have been recently found to exhibit pleiotropy includes PRR2, ATP1A3, ADCY5, GCH1 and SCL2A1 (GLUT1). These will be covered in the discussion that follows. In contrast to pleiotropy is genetic heterogeneity, where multiple different genes can cause the same clinical picture.

A textbook cannot hope to provide the latest information on pathophysiology or genetics, and, although these will be discussed at times, the main focus of this chapter will be clinical. A difficulty with an overview of movement disorders in childhood is that, apart from tics and stereotypes, the underlying conditions are usually uncommon, and are often rare. As Professor Aicardi has in previous editions of this book, we will concentrate on selected important conditions, supplemented by Tables. The topics that are discussed in more detail are chosen because of their clinical relevance, their response to treatment, or because they cover a relatively new or poorly understood area. As an example, although Wilson disease is rare in childhood, its clinical features are described in detail, as it is a disease that shadows the diagnosis of virtually every movement disorder of childhood.

**CLINICAL ASPECTS OF BASAL GANGLIA DISEASES**

Given the rapid advances in both genetics and imaging it is possible that in the future, words such as dystonia and chorea will have the same relevance to clinicians as ‘whispering pectoriloquy’ and ‘aeogophony’ have for today’s doctors. The child will simply be described as having a movement disorder (perhaps subdivided into hypo- or hyperkinetic), and sophisticated imaging and genetic studies will be used to make the diagnosis. This day is still some time away. Previous diagnostic advances, such as the arrival of computed tomography (CT) and then magnetic resonance imaging (MRI), were accompanied by suggestions that the physical examination of patients would become obsolete. This, of course, did not occur and we believe an understanding of the clinical features of the various movement disorders remains relevant.

As a general rule, movement disorders cease when the person goes to sleep. This includes even the extremely violent movements of hemiballismus. Paradoxically, the exception is tics which are in a sense the most ‘voluntary’ of movement
disorders, yet can be seen in multiple different stages of sleep (Cohrs et al. 2001).

The first difficulty in the diagnosis of movement disorders is found in the words themselves. It is important not to lose sight of the limitations of the words we use, and not to be intimidated by them. In the movement disorder lexicon, there are only a small number of terms such as dystonia, myoclonus, chorea, tremor, stereotypy and tics. These are applied to an extraordinarily wide variety of complex movements. These words are of an antiquity, with chorea being with us since 1686 and ‘modern’ terms such as dystonia and myoclonus more than 100 years old. Over time, the way these terms have been used has varied. It is also common for more than one movement disorder to be seen in the same patient. Diagnosis remains essentially clinical, and relies on the careful observation of the child. Neurophysiological testing is often not helpful in providing a clear label for a particular movement (Singer et al. 2010). With complex cases, a decision has to be made as to what seems to be the dominant, or most relevant, movement disorder. It must be recognised that even among so called experts in the field of movement disorders, disagreement is common. Treatment is influenced by the diagnosis, and therefore an accurate diagnosis is important. However, at times the movements present a mixed and confusing picture, and it is better to acknowledge this, than to insist that a particular word be applied, in what is essentially a futile attempt at self-reassurance.

In 1981, Professor Brian Neville observed: ‘The vast number of described diseases of the nervous system in childhood should not be allowed to disguise the low diagnostic rate’ (Neville 1981). The rate of diagnosis has improved in the last 30 years, but to paraphrase Professor Neville, the vast number of causes of abnormal movements in childhood should not be allowed to disguise the lack of effective treatment for so many of these diseases. In the following sections we discuss treatments, but unfortunately for many conditions, these are depressingly limited.

**BASAL GANGLIA RADIOLOGY**

The basal ganglia are no longer a dark basement of the brain, but are easily seen on MRI. It is important to have a good understanding of the MRI anatomy of the basal ganglia, as distinctive patterns of involvement can be very helpful in making a diagnosis. When describing MRI findings, rather than using terms such as ‘striatum’ and ‘lentiform nuclei’ which were coined before there was any real understanding of how the basal ganglia function, we feel it is preferable to name the individual structures involved. Detailed reviews of the anatomy of the basal ganglia are found in standard neuroanatomy texts. There have also been multiple articles dealing with the radiological anatomy and patterns of disease involvement in basal ganglia disorders (Anderson et al. 2004; Hathout 2009; Hegde et al. 2011; Bekiesinska-Figatowskaa et al. 2013). The following is a brief overview (Fig. 19.1).

The caudate nucleus (from cauda, Latin for tail) is medial to the internal capsule. It is a tadpole-like structure, and the caudate head is easily seen on MRI as it protrudes into the frontal horn of the lateral ventricle. With caudate atrophy the frontal horns appear dilated. The tapering body of the caudate is on the floor of the body of the ventricle, and the narrow tail follows the curve of the inferior horn. The putamen is located lateral to the internal capsule, just medial to the external capsule. The caudate and putamen share a common embryological origin, and are identical histologically. Small strands of grey matter cross the internal capsule, connecting the caudate head is easily seen on MRI as it protrudes into the frontal horn of the lateral ventricle. With caudate atrophy the frontal horns appear dilated. The tapering body of the caudate is on the floor of the body of the ventricle, and the narrow tail follows the curve of the inferior horn. The putamen is located lateral to the internal capsule, just medial to the external capsule. The caudate and putamen share a common embryological origin, and are identical histologically. Small strands of grey matter cross the internal capsule, connecting the caudate and putamen. Anteriorly, the head of the caudate and anterior edge of the putamen fuse, forming the nucleus accumbens.

The globus pallidus is embryologically and histologically distinct from the caudate and putamen. It is located medial to the putamen, with the two separated by a thin band of myelinated fibres called the lateral medullary lamina. The globus pallidus lies lateral to the internal capsule. The globus pallidus is divided into a larger external, and a smaller internal...
segment, separated by the medial medullary lamina. The substantia nigra is easily seen in the midbrain between the red nucleus and the corticospinal tract. It is also divided into two parts. The more ventral pars reticulata (SNr) functions almost as an extension and analogue of the globus pallidus interna. The more dorsal pars compacta (SNC) contains the dopamine secreting neurons. The subthalamic nucleus (STN) is a small, biconvex, lens-shaped nucleus that lies dorsolateral to the cranial end of the substantia nigra, and lateral to the cranial margin of the red nucleus. It is near the medial aspect of the internal capsule.

The red nucleus, globus pallidus interna and the SNr usually contain more iron than the surrounding structures, and are hypointense on T2-weighted images of older children. Account has to be taken of the changes that occur with development. For example, in the normal term infant, on T1-weighted images the STN is moderately hyperintense to the adjacent unmyelinated white matter (Bosemani et al. 2014). This T1-hyperintensity disappears over time. The STN becomes difficult to distinguish from the surrounding white matter on T1-weighted images, but becomes progressively hypointense on T2-weighted images due to increasing iron deposition.

At the end of this chapter, in Tables 19.15–19.21, we list distinctive patterns of basal ganglia involvement that may be very helpful in suggesting a diagnosis. Figures 19.3–19.13 show MRI scans with examples of basal ganglia involvement in different conditions.

As discussed above, in the descriptions of MRI we believe the actual structure should be named in the interest of accuracy and to avoid misunderstandings. The term ‘striatum’ refers to the caudate and putamen together. In descriptions of the basal ganglia circuitry, it is more convenient to use ‘striatum’, rather than naming the two component structures each time. However, elsewhere it can be a confusing term. There is a distinction between the ‘dorsal striatum’ involved in motor control, and the ‘ventral striatum’ which includes the nucleus accumbens, and is involved in non-motor functions such as reward-directed behaviour. The term ‘neostriatum’ has also been used to indicate the caudate and putamen, with ‘paleostriatum’ indicating the globus pallidus. ‘Lentiform nucleus’ is a term applied to the putamen and globus pallidus, as together they form a lens-like structure lateral to the internal capsule. However, they are quite different in their microscopic anatomy and their neurophysiology. There are also diseases that specifically target the globus pallidus (see Table 19.17). Describing the child as having ‘bilateral lesions of the globus pallidus interna’ is far more informative than saying there are ‘bilateral lesions of the lentiform nucleus’.

**BASAL GANGLIA CIRCUITS**

The basal ganglia circuitry is complex and for a more detailed description, there are many reviews (Mink 1996; DeLong and Wichmann 2007; Nambu 2008; Haynes and Haber 2013). The following is an over-simplification that may help the reader in beginning to understand how the basal ganglia are thought to work.

Basal ganglia circuitry basically consists of multiple parallel loops, travelling from the cortex to the basal ganglia, then on to the thalamus, before returning to the cortex (Alexander et al. 1986). Overall, the function of the motor loops of the basal ganglia is to enable movement but not to initiate it. The basal ganglia act by selecting a desired motor programme, and inhibiting other potentially interfering programs (Hwang 2013.) Input to the basal ganglia is from the cortex to the caudate, putamen, and the STN. Output is via the globus pallidus interna and the substantia nigra pars reticulata (usually taken together and referred to as GPI/SNr). The output is to the thalamus, and from there to the cortex. The basal ganglia output is a tonic inhibitory output. A reduction in this inhibition allows movement to take place via ‘released’ thalamocortical projections. (There are also projections from the GPi/SNr to the pedunculopontine nucleus and superior colliculi but these will not be discussed here.)

There appear to be three main pathways involved in the basal ganglia control of movement. [The hyperdirect pathway has mainly been studied in primates (Nambu et al. 2002). It is included here as there is frequent reference to it in the literature.]

- **The hyperdirect pathway:**
  - cortex → STN → GPI/SNr → thalamus → cortex

- **The direct pathway:**
  - cortex → striatum → GPi/SNr → thalamus → cortex

- **The indirect pathway:**
  - cortex → striatum → globus pallidus externa → STN → GPI/SNr → thalamus → cortex.

Stimulation of the direct pathway reduces inhibition of the thalamus, and allows movement. The other pathways increase or maintain inhibition of the thalamus, and restrict movement. Dopamine produced from the substantia nigra pars compacta and ventral tegmental area, modulates these pathways. An intricate co-ordination of these various components results in the production of a precise, selected movement.

There are multiple non-motor basal ganglia circuits. These are involved in human reasoning and adaptive function, the control of reward-based learning, and cognitive and emotional processes (Leisman et al. 2014). Therefore, it is not surprising that diseases of the basal ganglia can produce not only movement disorders, but psychiatric problems, such as obsessive–compulsive disorder and depression.

There is increasing interest in reciprocal pathways between the basal ganglia and the cerebellum. In primates there is a direct projection from the dentate nucleus to the dorsolateral putamen via the thalamus. The STN also connects to the cerebellum via the pontine nuclei. (For a review, see Kishore and Popa 2014.)
NEW CLASSIFICATION SCHEMES

The recent advances in genetics have resulted in a number of new classification schemes for movement disorders. The suggested new scheme for dystonia is discussed in the text. At the time of completion of this chapter, a paper suggesting a new nomenclature for genetic movement disorders was published (Matras et al. 2016). There appears to be much merit in this, but at times it is complex. For example, the condition that was once called neuroaxonal dystrophy, and then after the discovery of the gene, PLAN (PLA2G6-Associated Neurodegeneration), under this new scheme would be called NBIA/DYT/PARK-PLA2G6. To avoid potential confusion and the reader having to make frequent reference to this new paper, we have retained the ‘old’ terminology, realising that it may well be replaced by this new scheme in the next few years.

DYSTONIA

There has been a recent change in the definition of dystonia. It is now defined as ‘a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation’ (Albanese et al. 2013).

More than in any other movement disorder there can be confusion over the diagnosis of dystonia. Twisting of the limbs or trunk is the key clinical feature. The term torsion-spasm suggested by Flatau and Sterling in 1911 (Albanese et al. 2013), and subsequently employed by Wilson, nicely conveys the sense of sustained twisting of the body that separates dystonia from other movement disorders. However, what may not be appreciated, is that both children and adults with dystonia often also have fast movements. There may be repetitive jerking resembling a tremor, or isolated twitches that look like myoclonus.

Apart from the coexistence of sustained twisting movements and rapid jerking, there are many other traps in the diagnosis of dystonia. The term torsion-spasm suggested by Oppenheim in 1911 to indicate that hypotonia and hypertonia can co-exist. However, children with dystonia may have arms that feel floppy to the examiner, but as soon as the child makes an attempt to reach for an object, the tone increases and the arm twists due to excessive co-contraction of agonist and antagonistic muscles. The arm may then be jerked away from the target, or may twist in the opposite direction to what was intended.

In progressive generalised dystonia, over time the limbs generally develop increased tone at rest. Classically, the increased tone of dystonia is present throughout the range of movement, and is there when the arms are moved quickly or slowly (Sanger et al. 2003). There is considerable overlap between hypertonia due to dystonia, and rigidity, which is most commonly seen in adults with Parkinson disease, and where the term ‘lead-pipe’ rigidity is often used. In contrast, the characteristic feature of spasticity is that the increase in tone is velocity-dependent. An arm may be able to be moved slowly through a relatively wide range of motion, but with rapid movement there is a sudden increase in tone and the arm ‘catches’, suddenly resisting the movement. Dystonia and spasticity often co-exist, and this separation is not always easy in practice. Dystonia typically disappears during deep sleep.

However, with severe and prolonged disease, contractures can develop which will persist in sleep.

A good way of bringing out increased tone in milder forms of dystonia is to move the child’s arm back and forth slowly, and then ask the child to tap with the other arm. There is then suddenly an increase in tone in the arm that the examiner previously moved with little resistance. This manoeuvre also brings out parkinsonian rigidity. Rapidly pronating and supinating the affected arm has a similar effect.

A characteristic sign of dystonia in adults is the ‘geste antagonistique’ where touching a part of the body may reduce the intensity of the dystonia. For example, touching the side of the head may improve torticollis. Gestes are not commonly recognised in childhood. The term overflow refers to unintentional muscle contraction which occurs at the same time as the dystonic movement, but is anatomically distinct from it.

In dystonia there is usually an inability to suppress unwanted motor activity, resulting in excessive co-contraction of opposing muscle groups. This typically involves the same group of muscles, and so it appears in a specific distribution. The dystonic movements thus have a pattern. The term dystonic posturing is commonly used in descriptions of dystonia. Dystonic posturing can be defined as abnormal positions of the trunk or limbs, that result from the sustained co-contraction of opposing muscles. Dystonic postures are usually maintained for minutes or hours, but at times can be brought out by specific manoeuvres such as asking the patient to hold their arms up in front of them. The arms and fingers then twist. A common dystonic posture is an arm twisting up behind the back when walking. Dystonia can be mistaken for a psychogenic disorder, and the arm twisting behind the back while walking is a useful sign, as it is common in dystonia, but rare in psychogenic disorders. There are many other unusual postures that can occur in dystonia, such as the so called ‘flamingo’ stance, where the person is only able to stand on one leg, with the other flexed up against the trunk. These at times bizarre postures may also be mistakenly interpreted as psychogenic in origin.

It is important not to overuse the term dystonic posturing as similar postures can be seen in peripheral neuropathies and joint disease. In dystonia and other movement disorders such as chorea, children may hold themselves in a particular way that they have found reduces the severity of the movement...
disorder. So an apparent abnormality of posture may, in fact, be a position that the child has found allows better motor function.

There are certain specific dystonic syndromes that suggest the underlying cause. Severe oromandibular dystonia, especially with tongue biting is seen in neurodegeneration with brain iron accumulation syndromes (NBIA), and Lesch–Nyhan syndrome (discussed below). In young adults, neuroacanthocytosis and neuroleptic drug-induced dystonia are also causes. Action-induced dystonic opisthotonus, in which the trunk tends to arch backwards when the patient stands, and occasionally even when lying down and attempting to move, is also a feature that may be seen in the NBIA (Stamelou et al. 2013). An inability to produce words or sounds is associated with a relatively small number of dystonic syndromes (Ganos et al. 2016) – see Table 19.5.

The pathophysiology of dystonia is uncertain. Traditionally associated with abnormalities of the basal ganglia, it may be better seen as a network disorder involving multiple regions. There is currently considerable interest in the role of the cerebellum in the development of dystonia (Prudente et al. 2014).

**CLASSIFICATION OF DYSTONIA**

As well as suggesting a new definition of dystonia, Albanese et al. (2013) also suggested a new classification scheme. The diagnosis of dystonia can now be divided into two main axes: (1) the clinical features and (2) aetiology.

**Clinical Features of Dystonia**

The clinical features of dystonia can be approached in five different ways.

1. The first is the age at onset: infancy (birth to 2 years); childhood (3–12 years); adolescence (13–20 years); early adulthood (21–40 years); and late adulthood (>40 years).

2. Dystonia can also be classified according to its distribution. Discrete body regions involved by dystonia can be subdivided into: (a) the upper or lower cranial region, (b) the cervical region, (c) the larynx, (d) the trunk, (e) the upper limbs, and (f) the lower limbs. In focal dystonia, only one body region is affected. A typical example is blepharospasm. In segmental dystonia, two or more contiguous body regions are involved. An example is blepharospasm combined with dystonia of the lower face and jaw or tongue. In multifocal dystonia, two noncontiguous or more (contiguous or not) body regions are involved. In generalised dystonia, the trunk and at least two other sites are involved. Generalised forms with leg involvement are distinguished from those without leg involvement. A typical example of hemidystonia is a person with arm and leg dystonia on the same side of the body following a destructive lesion to the contralateral basal ganglia.

3. The third component is the temporal pattern, that is, whether the disease course is static or progressive, and whether there is variability in the symptoms such as diurnal variation. Albanese et al. (2013) make a distinction between paroxysmal dystonia which typically continues after the trigger has ended, and action dystonia which is no longer evident after the inducing action has been completed. For example, with paroxysmal kinesigenic dyskinesia, sudden movement provokes an episode of dyskinesia which can continue for 20 seconds, at a time when the child is no longer moving forward.

4. The fourth component is whether the dystonia is isolated or combined with another movement disorder such as myoclonus or parkinsonism. (If there is tremor, it is still considered to be an isolated dystonia.)

5. The fifth component is whether there are other neurologically or systemic manifestations.

In this scheme rather than the potentially confusing term ‘primary dystonia’ used previously, ‘isolated dystonia’ is preferred. The terms ‘dystonia plus’ and ‘heredodegenerative dystonias’ have been replaced by ‘combined dystonia’.

**Aetiology of Dystonia**

The second axis is aetiology. There are two main components: (1) the presence of nervous system pathology and (2) whether the condition is inherited, acquired or idiopathic. This part of the classification is more easily visualised in a Table (see Table 19.1). As always with movement disorders, words can be a problem. Those accustomed to a division into congenital meaning present at birth, versus acquired meaning occurring later, have to accept that acquired here effectively means a non-genetic disorder. A child who has an intrauterine stroke causing dystonia will have an acquired disorder. A condition that is idiopathic can be sporadic or familial, but if a causative gene is found, it will then be reclassified.

**GENETIC DYSTONIAS WITH ONSET IN CHILDHOOD**

A relatively small number of genetic dystonias have so far been identified. Table 19.2 lists the well-established genetic dystonias of childhood. There are multiple reviews of the genetics of dystonia (e.g. Klein 2014; Balint and Bhatia 2015; van Egmond et al. 2015; Marras et al. 2016) and the topic will be covered only briefly.

**DYT1** is the form of dystonia first described by Oppenheim in 1911 (Klein and Fahn 2013). Almost all cases are caused by a GAG deletion in the coding region of the *TOR1A* gene (Ozelius et al. 1997). It accounts for 80–90% of cases of generalised dystonia among the Ashkenazi Jewish population, but also occurs in people who are not Jewish. It is dominantly inherited, but with reduced penetrance. Only around 30% of those who carry the gene develop symptoms.
### Table 19.1  Dystonia classification: Aetiology

<table>
<thead>
<tr>
<th>Nervous system pathology</th>
<th>Inherited or acquired</th>
<th>Inherited</th>
<th>Acquired</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of degeneration</td>
<td>Inherited</td>
<td>Autosomal dominant</td>
<td>Perinatal brain injury</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Evidence of structural (often static) lesions</td>
<td>Autosomal recessive</td>
<td>Infection</td>
<td>Toxic</td>
<td>Familial</td>
</tr>
<tr>
<td>No evidence of degeneration or structural lesion</td>
<td>X-linked recessive</td>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mitochondrial</td>
<td>Neoplastic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychogenic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From Albanese et al. (2013).**

### Table 19.2  Genetic dystonias presenting in childhood

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Presentation</th>
<th>Inheritance</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>Early-onset generalised dystonia</td>
<td>AD</td>
<td>TOR1A</td>
</tr>
<tr>
<td>DYT2</td>
<td>Gen dystonia particularly upperbody</td>
<td>AR</td>
<td>HPCA</td>
</tr>
<tr>
<td>DYT4</td>
<td>Whispering dysphonia/ HABC</td>
<td>AD</td>
<td>TUBB4</td>
</tr>
<tr>
<td>DYT5a</td>
<td>Dopa-responsive dystonia</td>
<td>AD</td>
<td>GCH1</td>
</tr>
<tr>
<td>DYT5b</td>
<td>Dopa-responsive dystonia</td>
<td>AR</td>
<td>TH</td>
</tr>
<tr>
<td>DYT6</td>
<td>Adolescent-onset dystonia of mixed type</td>
<td>AD</td>
<td>THAP1</td>
</tr>
<tr>
<td>DYT8</td>
<td>Paroxysmal nonkinesigenic dyskinesia 1</td>
<td>AD</td>
<td>MRI</td>
</tr>
<tr>
<td>DYT10</td>
<td>Paroxysmal kinesigenic dyskinesia 1</td>
<td>AD</td>
<td>PRRT2</td>
</tr>
<tr>
<td>DYT11</td>
<td>Myoclonus-dystonia</td>
<td>AD</td>
<td>SGCE</td>
</tr>
<tr>
<td>DYT12</td>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>AD</td>
<td>ATP1A3</td>
</tr>
<tr>
<td>DYT16</td>
<td>Young-onset dystonia-parkinsonism</td>
<td>AR</td>
<td>PRKRA</td>
</tr>
<tr>
<td>DYT18</td>
<td>Paroxysmal exertion-induced dyskinesia 2</td>
<td>AD</td>
<td>SCL2A1</td>
</tr>
<tr>
<td>DYT24</td>
<td>Cranial-cervical dystonia, tremor</td>
<td>AD</td>
<td>ANO3</td>
</tr>
<tr>
<td>DYT25</td>
<td>Cranial-cervical dystonia</td>
<td>AD</td>
<td>GNAL</td>
</tr>
<tr>
<td>DYT27</td>
<td>Cranial-cervical dystonia</td>
<td>AR</td>
<td>COL6A3</td>
</tr>
</tbody>
</table>

**From Albanese et al. (2013).**

The clinical phenotype is variable. Some members of a family who carry the gene can be asymptomatic, whereas others are so severely affected that they develop status dystonicus (Opal et al. 2002). Onset of symptoms is commonly between 5 and 15 years, but onset as late as 64 years has been reported (Opal et al. 2002). In the younger child, the first sign is often inversion of the foot with plantar flexion when walking. Older children may present with arm involvement, and have difficulty with writing, or specific manual tasks. The symptoms may fluctuate and worsen with stress or anxiety, resulting in an initial suspicion of a psychogenic disorder. The dystonia usually generalises and can become very severe. Lordosis and trunk twisting are common. Intelligence is preserved. Prior to the development of the surgical techniques of pallidotomy and deep brain stimulation (DBS) of the GPi, many affected individuals become wheelchair dependent or bedridden, and were left with horrible distortions of the body. Life-threatening episodes of status dystonicus can also occur in patients with DYT1 dystonia (Allen et al. 2014).

Heiman et al. (2004) found that both manifesting and non-manifesting carriers of the DYT1 mutation had an increased risk of an early-onset, recurrent, major depressive disorder, suggesting that depression is another clinical expression of the gene mutation.

**DYT2**  A consanguineous family has been described with generalised dystonia most prominent in the upper half of the body and presenting in the first decade of life. Inheritance was autosomal recessive and the patients were found to have mutations in the HPCA gene (Charlesworth et al. 2015).

**DYT4**  Mutations in TUBB4 have been found in an Australian family with ‘whispering dysphonia’ (Lohmann et al. 2013). In addition, TUBB4 mutations have also been found to be responsible for the condition Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (HABC) where dystonia can be a very prominent and disabling feature (Simons et al. 2013) (Fig. 19.11). In some patients, the MRI appearance of HABC is virtually diagnostic, with hypomyelination, cerebellar atrophy and progressive loss of the putamen over time. However, this combination of radiological signs is not seen in all patients. In older individuals with HABC, there may be complete loss of speech (Ganos et al. 2016).

**DYT5a and DYT5b**  Before the underlying genetic abnormalities were identified, the terms ‘dopa-responsive dystonia’ or ‘Segawa syndrome’ were used to describe children with...
dystonia who had a dramatic and sustained response to L-dopa. The most common cause of DRD is a dominant mutation in the enzyme GTP cyclohydrolase1 (GCH1), which catalyses the first step in porin synthesis (Ichinose et al. 1994). Rarely, recessive mutations in the tyrosine hydroxylase (TH) gene are responsible (Ludecke et al. 1995). (Inborn errors of dopamine metabolism, and other dopa-responsive disorders are covered in detail in the Parkinsonism section of this chapter.)

In classic Segawa syndrome, the child presents in the first decade of life with dystonia that shows diurnal variation (Segawa et al. 1976). After an overnight sleep or a daytime nap, the child seems normal but within an hour or so dystonia appears, and continues to increase during the day. (A perhaps apocryphal description of this condition is that the child can walk to school, but has to come home in a wheelchair.) The dystonia typically affects the legs, and onset is usually around 6 years of age. There is a strong female predominance. Symptoms are reversed by L-dopa therapy usually in relatively low doses. With Segawa syndrome, even if the diagnosis is delayed by more than 40 years, there can be a good response to treatment (Harwood et al. 1994).

Not all children with GCH1 deficiency have the typical clinical picture. There may be no diurnal variation. Usually the reflexes are brisk, and the Babinski sign may appear positive. As a result the child may be mislabelled as having ‘cerebral palsy’ (CP) (Boyd and Patterson 1989; Fletcher et al. 1993). Tremor can predominate, and the presentation may be with exercise-induced dystonia (Dale et al. 2010). There is a report of a 17-year-old boy with with GCH1 deficiency presenting as a myoclonus-dystonia syndrome (Leuzzi et al. 2002). When the onset of the disease is in adulthood, the presentation of GCH1 deficiency includes writer’s cramp, torticollis and postural tremor (Segawa 2011). Recreational forms of GCH1 deficiency can present in infancy with a dystonia/parkinsonism syndrome (Furukawa et al. 1998; Nardocci et al. 2003).

**DYT6** is caused by mutations in mutations in the THAP domain containing 1 (THAP 1) gene. It is inherited as an autosomal dominant condition with penetrance of around 40%. The clinical presentation can overlap with DYT1 dystonia, but the onset is usually later. In addition, in contrast to DYT1 dystonia, there is frequent involvement of the cranial muscles with speech commonly affected by oromandibular dystonia or laryngeal dystonia (Segawa 2011). Recreational forms of GCH1 deficiency can present in infancy with a dystonia/parkinsonism syndrome (Furukawa et al. 1998; Nardocci et al. 2003).

**DYT11 – Myoclonus Dystonia** is a dominant condition where myoclonus and dystonia co-exist. It is mainly due to mutations in the epsilon sarcoglycan (SGCE) gene. With SGCE mutations, genetic imprinting reduces the penetrance when the gene is inherited from the mother. Myoclonus is often the earliest feature and may remain the only manifestation. The myoclonus typically involves the upper limbs, with at times quite violent shock-like jerks that may be action-induced. It appears to be a subcortical form of myoclonus. Dystonia is often mild. In younger children, leg dystonia may be prominent and transient (Kyllerman et al. 1993), whereas in adults, the upper body is more involved. The jerks may be reduced by alcohol ingestion. Depression, obsessive-compulsive symptoms, anxiety and panic attacks may be prominent (Peall et al. 2013). Large deletions involving SGCE and the contiguous COL1A2 gene cause, in addition, associated skeletal problems and osteoporosis (Asmus et al. 2007a). Zonisamide may have an important role in the treatment of myoclonus dystonia reducing both myoclonus and dystonia (Hainque et al. 2016).

There have been reports of families with the myoclonus dystonia phenotype due to mutations in KCTD17 (Mencacci et al. 2015a) and CACNA1B (Groen et al. 2015). Some members of the family with the CACNA1B mutations had addition problems not usually seen in myoclonus dystonia, including unsteadiness while standing due to high-frequency continuous myoclonus in the legs, cardiac arrhythmias, and episodes of painful cramps in upper and lower limbs.

**DYT12** also known as rapid onset dystonia-parkinsonism (RODP) is caused by a mutation in the ATP1A3 gene (de Carvalho Aguiar et al. 2004). Typically in adolescence there is a rapid onset of dystonia and parkinsonism which appear over hours or weeks. The onset often appears to be provoked by emotional or physical distress, and the disability is permanent. Again there is craniofacial involvement with oromandibular dystonia, facial involvement and dysphagia, and at times typical parkinsonian features (Brashear et al. 2007). There is usually minimal or no tremor at onset. With RODP, once the symptoms have been present for around a month, there is usually no further deterioration, except for rare ‘second onsets’, or abrupt worsening of symptoms later in life (Brashear et al. 2007). The parkinsonism does not respond to L-dopa. When the onset of symptoms is over several weeks and follows an emotional trauma, children in the 10–14-year age range with ATP1A3 mutations, are at risk of being diagnosed as having a psychogenic problem, as signs such as a geste may be misinterpreted.

Brashear et al. (2012) reported a child with an ATP1A3 mutation who presented at 9 months of age with fluctuating episodes of hypotonia and ataxia, followed by the development of oromandibular dystonia. There are other disorders that have been found to be associated with ATP1A3 gene mutations including alternating hemiplegia of childhood (Heinzen et al. 2012), and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss) (Demos et al. 2014). Mutations in ATP1A3 have also been found in a child who developed seizures 4 hours after birth and went on to have an intractable seizure disorder with episodes of status epilepticus, and another child with seizures beginning from 6 weeks followed by recurrent episodes of prolonged apnoea required tracheostomy (Paciorkowski et al. 2015). Also reported in association with ATP1A3 mutations are children with presentations intermediate between alternating hemiplegia of childhood and RODP, including the
presence of dopa-responsive oculogyric crises (Termsarasab et al. 2015). Adult patients with an ATP1A3 mutation may have a relapsing encephalopathy characterised by recurrent episodes of cerebellar ataxia and altered consciousness during febrile illnesses (Dard et al. 2015). With presentations from the neonatal period to adult life, and multiple different clinical scenarios, ATP1A3 mutations illustrate how much genetic advances have overturned previous concepts, in particular the ‘one gene, one phenotype’ hypothesis.

**DYT16** is caused by mutations in the gene **PRKRA** and has autosomal recessive inheritance (Camargos et al. 2008). There is generalised, early-onset dystonia with axial muscle involvement, oromandibular and laryngeal dystonia and, in some cases, parkinsonian features that do not respond to L-dopa therapy. The initial report was in 2008, describing two unrelated Brazilian families. Subsequently a child was described who had an early, acute presentation with hypotonia, bradykinesia, pyramidal signs, and developmental regression associated with a febrile illness (Leemon et al. 2013). At 18 months of age, he was noted to have limb dystonia, and a progressive dystonia followed with involvement of the trunk, oromandibular and cervical regions and limbs. There was a transient response to biotin. MRI showed progressive loss of the caudate, putamen and globus pallidus. There was also white matter loss. Further reports of Polish (Zech et al. 2014) and Brazilian families (de Carvalho Aguiar et al. 2015) have confirmed that **PRKRA** mutations are pathogenic and can also cause isolated dystonia.

**DYT24** is caused by **ANO3** mutations. The age at onset can vary from early childhood to the forties (Stamelou et al. 2014). Cervical and laryngeal dystonia are the usual presenting features. The presentation is similar to DYT6, except that in DYT24, tremor is frequently seen. At times tremor can be the sole initial manifestation, leading to a misdiagnosis of essential tremor.

**DYT25** caused by **GNAL** mutations, is another cause of cervical and oromandibular dystonia where onset can be in childhood (Fuchs et al. 2013). Loss of the sense of smell may be a clue to the diagnosis (Balint and Bhatia 2015).

**DYT27** is caused by mutations in the a3 (VI) collagen gene **COL6A3** (Jochim et al. 2016). It is the third form of dystonia showing recessive inheritance. Clinical features include tremulous cervical, oromandibular, laryngeal, upper limb and trunk dystonia. Only a few patients have been described but one developed writer’s cramp at the age of 6 years (Jochim et al. 2016).

At the time of writing the condition had not yet been allocated a DYT ‘number’, but Meyer et al. (2017) have described 27 patients with a childhood-onset dystonia due to mutations in the histone methyltransferase gene, **KMT2B**. The median age at onset was 4 years, with most patients having lower limb dystonia at onset. With increasing age, the dystonia generalised with cervical, facial, and oromandibular dystonia producing dysarthria or anarthria (see also Table 19.5), and difficulties in chewing and swallowing. Severe dysphonia could also develop. Dysmorphic features were seen, including a characteristic elongated face and bulbous nasal tip. Subtle, symmetrical abnormalities of the globus pallidi were noted on MRI. Ten patients showed a good response to bilateral DBS of the GPi. There seems little doubt that over the next 10 years, as next generation sequencing becomes widely available, many new dystonia genes will be found.

In terms of the recent classification, DYT1 and DYT6 are considered isolated dystonias, whereas DYT5, DYT11 and DYT12 are combined dystonias (Klein 2014).

The paroxysmal dystonias DYT8 and DYT10, are discussed in Chapter 16.

### NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

The term neurodegeneration with brain iron accumulation (NBIA) is used for a group of conditions characterised by movement disorders, progressive neurodegeneration and iron accumulation in the basal ganglia (Hogarth 2015). Dystonia is commonly seen, and therefore these disorders are discussed in the Dystonia section of the chapter. However, spasticity is also a common finding in this group of disorders. Other features include parkinsonism and intellectual decline. On MRI there is usually a symmetrical increase in iron content in those grey matter nuclei that normally contain more iron than other parts of the brain. These include the globus pallidus, substantia nigra, red nucleus, dentate nucleus, putamen and thalamus. Areas rich in iron are hypointense on T2-weighted sequences, and isointense on T1 sequences. T2*-weighted acquisitions such as gradient-echo sequences may accentuate this degree of hypointensity, and may be helpful in identifying NBIA disorders, as may susceptibility-weighted images. Iron typically appears markedly hypointense on both standard diffusion-weighted and apparent diffusion coefficient sequences (Krueer et al. 2012). In NBIA, the changes are usually symmetrical. When the MRI is performed using magnets of increased strength such as 3T and beyond, it is important to remember that normal iron containing structures will appear more prominent than in scans where magnets of lesser strength were used.

Most of the major NBIA subtypes of childhood are autosomal recessive disorders, except beta propeller associated neurodegeneration (BPAN), which shows an X-linked pattern of inheritance.

### PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

Pantothenate kinase-associated neurodegeneration (PKAN) is the most frequently encountered form of NBIA, but is...
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Some caution is needed in interpreting this sign. The typical MRI finding in PKAN is the so-called ‘eye of the tiger’ sign. This is seen on T2-weighted sequences. The globus pallidus is hypointense with an anteromedially placed region of hyperintensity representing the ‘eye’. Pathologically, an area of neuronal depletion and tissue rarefaction corresponds to the area of bright signal. Relatively early in the course of the illness, there may only be hypointensity of the globus pallidus without any eye of the tiger sign seen, and a mitochondrial disorder, or some other metabolic problem may be suspected. Conversely, the ‘eye of the tiger’ sign has been found in pre-symptomatic, mutation-positive children, identified after a sibling has been diagnosed with PKAN (Hayflick et al. 2001). There are also eye of the tiger ‘mimics’ including membrane protein associated neurodegeneration (MPAN), COASY protein-associated neurodegeneration (CoPAN), carbon monoxide poisoning survivors, multiple system atrophy and neuroferritinopathy (Hogarth 2015). Therefore, some caution is needed in interpreting this sign.

PLA2G6-ASSOCIATED NEURODEGENERATION

PLA2G6-Associated Neurodegeneration (PLAN; NAD: PARK14) is caused by mutations in the gene encoding calcium-independent phospholipase A2 (PLA2G6) (Figs 19.6a and 19.6b). The disease can present as classic infantile neuroaxonal dystrophy (INAD), atypical NAD, and PLA2G6-related dystonia-parkinsonism (Kurian and Hayflick 2013). INAD presents around the age of 14–18 months, and the child is never able to walk independently (Adams and Lyon 1982a). There is developmental arrest, then regression of language and motor skills. Affected children typically show a combination of upper and lower motor neurone signs, with the reflexes then being lost. There may be profound hypotonia and marked leg wasting. Optic atrophy leads to blindness, and dementia is usually relentlessly progressive. Seizures sometimes occur. On electroencephalogram (EEG) there may be prominent fast activity. Dystonia tends to be milder than in PKAN. Atypical NAD may present more with ataxia than spasticity, and the phenotype is not as severe as the infantile form. The adult form of PLAN presents with dystonia-parkinsonism and spasticity, along with cognitive and psychiatric features (Paisan-Ruiz et al. 2009). There may initially be a good response to L-dopa followed by disabling dyskinesias.

Cerebellar atrophy is the most common neuroimaging finding in both INAD and atypical NAD. It is present in most patients even early in disease, and in almost all well-established INAD cases (Hogarth 2015). Iron accumulation may not be seen on MRI in young onset cases. In later onset cases, the substantia nigra may be more heavily involved than the globus pallidus.

FATTY ACID HYDROXYLASE-ASSOCIATED NEURODEGENERATION

Fatty acid hydroxylase-associated neurodegeneration (FAHN) is caused by mutations in FA2H (Krue et al. 2010). It has clinical similarities to NAD. The first signs are usually focal dystonia and gait impairment. Other features include ataxia, progressive spastic quadriaparesis, and optic atrophy. Intellect may be relatively spared. Neuroimaging features of FAHN include increased iron in the globus pallidus and substantia nigra, but this is not always present. There may be confluent subcortical and periventricular white matter T2 hyper-intensities, along with thinning of the corpus callosum. Cerebellar and brain stem atrophy are progressive and severe (Hogarth 2015).

MITOCHONDRIAL MEMBRANE PROTEIN ASSOCIATED NEURODEGENERATION

Mitochondrial membrane protein associated neurodegeneration (MPAN) is caused by mutations in an open-reading frame on chromosome 19 (C19orf12) (Hogarth et al. 2013).
MPAN usually manifests as a juvenile-onset, slowly progressive disorder with predominant lower limb spasticity and cognitive impairment. Dystonia may be limited to the hands and feet (Hogarth 2015). The mean age at onset is around 10 years. Typical additional features include axonal motor neuropathy, which is a distinctive feature of MPAN (Schottmann et al. 2014), and optic atrophy. In adults the disease may be rapidly progressive (Dogu et al. 2013). MPAN is also reported to cause a parkinsonism-pyramidal syndrome (Krueger et al. 2014).

MRI in MPAN shows iron deposition in the globus pallidus and substantia nigra. In some cases, hyperintense streaking of the medial medullary lamina is seen and may discriminate MPAN from other NBIA subtypes (Hartig et al. 2013). (The medial medullary lamina separates the internal and external segments of the globus pallidus.)

**KUFOR-RAKEB SYNDROME**

Kufor-Rakeb syndrome (KRS) (PARK 9) is caused by mutations in the ATP13A2 gene. In the initial report, typical features included parkinsonism, pyramidal signs, a supranuclear palsy with upgaze paresis, and dementia (Nisipeanu et al. 1994). There was a rapid progression to a bedridden state within 12 months. Rest tremor was absent. Bradykinesia and rigidity were exquisitely sensitive to levodopa, but it had no effect on the pyramidal signs. At subsequent review of the family, it became clear that L-dopa therapy was limited by the development of dyskinesia. Other clinical features that have been noted included mini-myoclonus involving the face, tongue and fingers, visual hallucinations, and oculogyric crises (Williams et al. 2005; Behrens et al. 2010.) Aggression and episodes of psychosis, including frank hallucinations, may occur. MRI show generalised cerebral, cerebellar and brain stem atrophy, along with progressive atrophy of the pyramids. There may also be iron deposition in the globus pallidus, caudate and putamen.

**BETA PROPELLER ASSOCIATED NEURODEGENERATION**

BPAN was initially called static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), a name that clearly evokes the clinical course. The disease is caused by mutations in WDR45 located on the X chromosome, which encode for a beta propeller protein that has a presumed critical function in autophagy (Haack et al. 2012). Being X-linked dominant, in theory it should be lethal in males, but there are reported male cases and the genetics must be complex (Hogarth 2015). BPAN begins with early childhood intellectual impairment which can be severe. Common early comorbidities include seizures, spasticity and disordered sleep. The course is then static, sometimes for decades. In adulthood, severe dystonia and parkinsonism develop. As with PLAN and Kufor-Rakeb syndrome, L-dopa treatment may initially improve the parkinsonism, but disabling dyskinesias rapidly develop, and it has to be discontinued.

On brain MRI, with T2-weighted sequences the substantia nigra and globus pallidus are hypointense consistent with iron deposition. In the substantia nigra, a linear streak is seen. On T1 sequences, this same area of the substantia nigra is surrounded by a hyperintense ‘halo’ extending to the cerebral peduncles, thought to represent neuromelanin release from degenerating neurons (Krueger et al. 2012). Significant cerebral and milder cerebellar atrophy are also seen. Basal ganglia calcification has been reported with BPAN (Van Goethem et al. 2014).

**COASY PROTEIN-ASSOCIATED NEURODEGENERATION**

COPAN is caused by mutations in the coenzyme A synthase gene (COASY) and is in the same metabolic pathway as the defect in PKAN (Dusi et al. 2014). Only a small number of cases have been described, but a pattern typical of the NBIA, of oromanibular dystonia, progressive spasticity, neuropathy, and then parkinsonism is seen. MRI demonstrates non-homogenous T2 pallidal hypointensity, with a region of medial hyperintensity that is reminiscent of the ‘eye of the tiger’ sign seen in PKAN (Hogarth 2015).

Summary of Neurodegeneration with Brain Iron Accumulation Syndromes

The NBIA are a rare to ultra-rare group of disorders that nevertheless have the potential to teach us much about brain function. Although iron deposition is a characteristic feature, this may not be pathogenic. Only experts in the area are likely to easily remember the distinctive clinical and radiological profiles of each condition. However, there are common features including movement disorders, spasticity and neuropathies. Dystonia and parkinsonism are the usual movement disorders. With PLAN, BPAN and KRS there may be L-dopa responsiveness but this is followed by intolerable dyskinesias. The diagnosis of NBIA can be suspected clinically, but MRI findings are most likely to point to the correct diagnosis. (Table 19.3 summarises some distinctive MRI features.) As a group, these conditions do not respond well to treatment. However, DBS can lessen the severity of the dystonia, and improve the quality of life (Timmermann et al. 2010).

**OTHER CONDITIONS THAT MAY PRESENT WITH DYSTONIA**

The genetic dystonias described above, are relatively rare. Dystonia is more commonly seen in the setting of CP where
Chapter 19 Basal Ganglia Diseases and Movement Disorders

Table 19.3 Radiological clues to the diagnosis of NBIA

<table>
<thead>
<tr>
<th>Radiological feature</th>
<th>Code</th>
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<tbody>
<tr>
<td>‘Eye of the tiger’ sign</td>
<td>PKAN</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>PLAN</td>
</tr>
<tr>
<td>Brainstem atrophy</td>
<td>FAHN</td>
</tr>
<tr>
<td>Hyperintense streaking of the medial medullary lamina</td>
<td>MPAN</td>
</tr>
<tr>
<td>Substantia nigra halo</td>
<td>BPAN</td>
</tr>
</tbody>
</table>

NBIA, neurodegeneration with brain iron accumulation.

Lesch–Nyhan disease (LND) is an X-linked recessive disorder caused by deficiency of hypoxanthine guanine phosphoribosyltransferase. This enzyme is involved in the recycling of the purine bases, hypoxanthine and guanine, back into the purine nucleotide pools (Nyhan 1997). The resultant elevated uric acid levels may result in orange, sand-like crystals of uric acid in the nappies of an affected infant. Haematuria may also be an early feature.

In the first 6 months of life, the infant typically is hypotonic and has delayed motor development. Involuntary movements usually develop between 6 and 24 months of age. Patients with LND are classically described as having choreoathetosis, but in a review of 44 patients, dystonia was present in all, and was the most severe movement disorder (Jinnah et al. 2006). Other movement disorders noted in this study included dystonia, and the diagnosis rested on the finding at postmortem of symmetrical degeneration of the caudate, putamen, and sometimes globus pallidus (Röyttä et al. 1981). With the advent of modern neuroimaging, it became clear there were milder cases, and many different causes, including infections and metabolic abnormalities (Dale et al. 2002). There were also variable outcomes.

Genetic causes of IBSN include mutations in mitochondrial genes (ATP6, ND1, ND67 and NDUFV1), and in NUP62 which codes for a nuclear pore complex protein. Other causes are thiamine transporter-2 deficiency, glutaryl-CoA dehydrogenase deficiency and mutations in the ADARI gene (Livingston et al. 2014). ADARI is the gene encoding the editing protein adenosine deaminase, which is involved in the recognition of self versus non-self double stranded RNA.

Mutations in ADARI are an example of a ‘type 1 interferonopath’ where aberrant stimulation or unregulated control of the system, leads to inappropriate and/or excessive interferon output (Crow 2011). Testing for elevated interferons
is technically difficult. An elevated cerebrospinal fluid (CSF) neopterin is a non-specific measure, but upregulation of interferon-stimulated genes (ISGs), the so called ‘interferon signature’ can be used as a measure of increased interferon activity (Livingston et al. 2014).

**TREATMENT OF DYSTONIA**

Dystonia is a difficult condition to treat. This is not surprising given our current lack of knowledge of its pathophysiology, and the many different causes of dystonia. There are many potential abnormalities that might contribute to the development of dystonia including: abnormal inhibition, altered plasticity, macroscopic or microscopic structural alterations in the striatum and its connections, abnormalities of cerebellar input, dopamine dysfunction, and abnormalities of function associated with cholinergic, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA), N-methyl-D-aspartate receptor (NMDA), gamma-aminobutyric acid receptor (GABA) and glutamate receptors (Breakefield et al. 2008). In an individual patient we usually have no idea which of these many potential factors could be operative.

A comprehensive review of the treatment of dystonia in childhood has recently been published by Roubertie et al. (2012). A widely practised approach in children with generalised dystonia is to first give the child L-dopa. If this fails, then the next drug is an anticholinergic such as trihexyphenidyl (also known as benzhexol). Further attempts at treatment are influenced by the clinical features of the child and include botulinum injections, oral baclofen, low-dose benzodiazepines, a number of newer oral agents, and DBS. Rehabilitation measures are important, but are usually not the province of the neurologist and are too vast a subject to be discussed here.

### Trial of L-dopa

In children with an inborn error of dopamine metabolism such as GCH1 deficiency, treatment with L-dopa can be dramatically effective. Therefore, a trial of L-dopa should be

<table>
<thead>
<tr>
<th>Table 19.4 Some causes of dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma</strong></td>
</tr>
<tr>
<td>Head trauma is a common cause of dystonia. The issue of peripheral injury to, for example, a foot giving rise to a focal or generalised dystonia remains controversial.</td>
</tr>
<tr>
<td><strong>Infarction of the basal ganglia</strong></td>
</tr>
<tr>
<td>The onset of dystonia may be delayed by months or years.</td>
</tr>
<tr>
<td><strong>Infectious or inflammatory causes</strong></td>
</tr>
<tr>
<td>Viral (or bacterial) vasculitis, especially varicella</td>
</tr>
<tr>
<td>AIDS encephalopathy and/or vasculopathy</td>
</tr>
<tr>
<td>Infectious encephalitis (EBV, mycoplasma, varicella, enterovirus, Group A Streptococcus)</td>
</tr>
<tr>
<td>Autoimmune encephalitis (anti-NMDAR encephalitis, basal ganglia encephalitis)</td>
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<tr>
<td><strong>Toxic causes</strong></td>
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<tr>
<td>Drug-induced dystonia (phenothiazines, anticonvulsants)</td>
</tr>
<tr>
<td>Anoxia/hypoxia of pre- or post-natal origin</td>
</tr>
<tr>
<td><strong>Metabolic/genetic/degenerative causes</strong></td>
</tr>
<tr>
<td>DYT1–DYT27</td>
</tr>
<tr>
<td>Wilson disease</td>
</tr>
<tr>
<td>Glutaric aciduria type I</td>
</tr>
<tr>
<td>Other organic acidemias</td>
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<tr>
<td>Amino acid disorders</td>
</tr>
<tr>
<td>Mitochondrial disorders (Leber optic atrophy, multiple causes of Leigh syndrome, SURF1 mutations)</td>
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<tr>
<td>Pyruvate dehydrogenase deficiency</td>
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<tr>
<td>Carnitine deficiency</td>
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<tr>
<td>Leukodystrophies (some forms)</td>
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<tr>
<td>Neuronal ceroid-lipofuscinosis</td>
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<tr>
<td>Fucosidosis (Fig. 19.4)</td>
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<tr>
<td>Hartnup disease</td>
</tr>
<tr>
<td>Idiopathic hypoparathyroidism</td>
</tr>
<tr>
<td>Gaucher disease</td>
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<tr>
<td>Niemann–Pick disease (type C in particular)</td>
</tr>
<tr>
<td>Thiamine transporter deficiency type 2</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type 1V (Morquio syndrome)</td>
</tr>
<tr>
<td>Lesch–Nyhan syndrome</td>
</tr>
<tr>
<td>Carbohydrate-deficient glycoprotein syndrome</td>
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<tr>
<td>Manganese accumulation</td>
</tr>
<tr>
<td>Infantile bilateral striatal necrosis (multiple causes)</td>
</tr>
<tr>
<td>HABC syndrome (Fig. 19.11)</td>
</tr>
<tr>
<td>Huntington disease</td>
</tr>
<tr>
<td>Dentatorubropallidolysian atrophy</td>
</tr>
<tr>
<td>Progressive calcification of the basal ganglia</td>
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<tr>
<td>Pelizaeus–Merzbacher disease</td>
</tr>
<tr>
<td>Neuronal Intranuclear inclusion disease</td>
</tr>
<tr>
<td>Deafness–Dystonia syndrome (Mohr–Tranebjaerg syndrome)</td>
</tr>
<tr>
<td>Ataxia–telangiectasia and variants</td>
</tr>
<tr>
<td>Vitamin E deficiency (mutations in the apha-tocopherol transfer protein)</td>
</tr>
<tr>
<td>KMT2B mutations</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>Tumours of the basal ganglia</td>
</tr>
</tbody>
</table>

EBV, Epstein-Barr virus; NMDAR, N-methyl-D-aspartate receptor; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum.
considered in any child with unexplained dystonia. In older children with GCH1 deficiency, dyskinesia is generally not a problem and the introduction of L-dopa does not require the slow escalation that is usually required in infancy. (This is covered in detail in the Parkinsonism section.) The starting dose of L-dopa (with a dopa-decarboxylase inhibitor) is around 1mg/kg/day with a target dose of 5mg/kg/day or higher. In typical GCH1 deficiency, doses of between 50–100mg of L-dopa, given two to three times a day, will often be sufficient to make the child essentially normal. As GCH1 is a cofactor in both dopamine and serotonin metabolism, brain serotonin levels potentially are low. However, 5-OH tryptophan has generally not been added to L-dopa, as depression and other potential manifestations of serotonin deficiency do not seem to be common clinical problems in typical GCH1 deficiency (Segawa 2011). Consistent with the clinical impression, Furukawa et al. (2016) found at postmortem in the striatum of a patient with GCH1 deficiency, very low levels of dopamine but normal concentrations of serotonin.

Most children with unexplained dystonia will not have an inborn error of dopamine metabolism, and this raises the difficult question of how high a dose of L-dopa should be given, and for how long should the trial continue? If the child has been on L-dopa (with a dopa-decarboxylase inhibitor) in a dose of 5mg/kg/day for several months with no substantial clinical response, then generally speaking, it is unlikely that continuing with it will make a significant difference.

A difficulty with the L-dopa trial is that dopamine may produce some improvement in dystonia even when the child does not have an inborn error, including in the setting of CP (Brunstrom et al. 2000). A not uncommon situation is a child with dystonia started on L-dopa, who to the examiner’s mind has not dramatically changed, but the parents feel has a better quality of life while taking it. There is a longstanding concern that L-dopa, because of its propensity to promote the formation of cytotoxic free radicals and other reactive oxygen species, might be neurotoxic. In the much more common situation of the treatment of adults with Parkinson disease, this has not yet been fully resolved (Olanow 2015). As the brains of children may be more vulnerable to oxidative stress than adults, caution is warranted in the long-term use of L-dopa. When the problem is an inborn error of dopamine metabolism, and treatment is aimed at returning low brain dopamine levels to their normal range, the risk would seem low. In those children who have shown questionable improvement, it is important not to simply leave the child on long-term L-dopa based on an initial good impression, but to periodically question its efficacy.

Other Treatments

Our impression is that trihexyphenidyl is the drug most likely to be effective if the L-dopa trial has failed. There is experimental support for the use of trihexyphenidyl as it has been found to correct synaptic plasticity deficits in the striatum of mice with the DYT1 dystonia mutation (Maltese et al. 2014). There is also clinical evidence to support its efficacy (Balash and Giladi 2004). However, some patients initially classified as primary torsion dystonia who had a good response to anticholinergic therapy, were subsequently found to have GCH1 deficiency (Jarman et al. 1997a), which makes assessment of the older literature difficult. With anticholinergics, a 'start low and go slow approach' is recommended with a starting dose as low as 0.03mg/kg/day. In the past, doses of trihexyphenidyl of 40–80mg per day have been used (Fahn 1983). In children who are essentially helpless because of severe motor disability, it is difficult to assess side effects such as cognitive impairment, drowsiness, dry mouth, blurred vision, and constipation. We would suggest these high doses should only be used if there is compelling evidence of efficacy. Urinary retention is an additional potential side effect.

Oral baclofen may be helpful with dystonia but can worsen pre-existing hypotonia (Roubertie et al. 2012). Intrathecal baclofen is used for severe generalised dystonia, but the evidence of its efficacy is not as impressive as it is in the treatment of spasticity (Berweck et al. 2014). Because of the technical difficulties involved, its use should be confined to specialised centres with considerable expertise.

Tetrabenazine (TBZ) has a complex pharmacology, and although sometimes used for dystonia, it is more commonly used for hyperkinetic movement disorders such as chorea (Jankovic and Oman 1988; Jain et al. 2006; Gras et al. 2012). The main action of TBZ and its active metabolites is to

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**Table 19.5** Dystonia with Anarthria/Aphonia

<table>
<thead>
<tr>
<th>Inborn errors of dopamine metabolism (aromatic acid decarboxylase deficiency, tyrosine hydroxylase deficiency, sepiapterin reductase deficiency, dopamine transporter deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEGDEL syndrome (SERAC1 gene mutations)</td>
</tr>
<tr>
<td>FOXG1 mutations</td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
</tr>
<tr>
<td>Glutaric aciduria type 1</td>
</tr>
<tr>
<td>NBIA syndromes (PKAN, MPAN, PLAN)</td>
</tr>
<tr>
<td>Kernicterus (Fig. 19.7)</td>
</tr>
<tr>
<td>HABC syndrome (TUBB4 mutations)</td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
</tr>
<tr>
<td>Niemann–Pick type C</td>
</tr>
<tr>
<td>DYT12</td>
</tr>
<tr>
<td>DYT16</td>
</tr>
<tr>
<td>Wilson disease</td>
</tr>
<tr>
<td>KMT2B mutations</td>
</tr>
</tbody>
</table>

From Ganos et al. (2016). MEGDEL, 3-methylglutaconic aciduria with sensori-neural deafness, encephalopathy, and Leigh-like syndrome; NBIA, neurodegeneration with brain iron accumulation; PKAN, Pantetheinase kinase-associated neurodegeneration; MPAN, membrane protein associated neurodegeneration; PLAN, PLAXG6-associated neurodegeneration; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum.
reversibly inhibit the human vesicular monoamine transporter 2, which transports monoamines such as dopamine, serotonin, and norepinephrine from the cellular cytoplasm into synaptic vesicles (Chen et al. 2012). Therefore, it potentially has profound effects on the function of dopamine and other neurotransmitters. Dose-limiting adverse effects include somnolence, insomnia, fatigue, depression, akathisia, anxiety and nausea. TBZ has also caused parkinsonism and oculogyric crises (Janik and Figura 2016). Life threatening complications include hyperthermia, neuroleptic malignant syndrome, severe dysphagia and suicide (Chen et al. 2012). If tetrabenzine is used, we recommend caution, and it should be continued only when there is a convincing demonstration of its efficacy.

A recent retrospective study has suggested neuronin has a role in children with very severe dystonia (Loiw et al. 2016). Improvements were seen in the ability of the child to sit, the frequency of involuntary muscle contractions, general muscle tone, and the duration and quality of sleep. There was also less pain and improved mood.

As discussed briefly above, in a controlled study of 23 patients with myoclonus-dystonia syndrome, zonisamide was shown to improve both myoclonus and dystonia (Hainque et al. 2016). (Eighteen of the patients had mutations in the epsilon sarcoglycan gene.)

Most children who receive botulinum toxin injections have a generalised dystonia often with coexistent spasticity. The injections are targeted at particularly troublesome areas, such as when there is painful muscle spasm (Guettard et al. 2009). Although the injections need to be repeated every 3–6 months, our impression is that this is of benefit, and safe.

**Deep Brain Stimulation**

This is a huge and complex subject and can only be dealt with briefly. (For a review, see Cif and Coubes 2016.) If a child has a genetic dystonia, such as DYT1, DBS of the GPi can be extraordinarily effective, returning a severely incapacitated child to near normality (Cif et al. 2003). Unfortunately, most children have an acquired form of dystonia, usually in the setting of CP, and have sustained damage to the basal ganglia. They often have other movement disorders, and also spasticity. When children with acquired dystonia are treated with DBS, scales developed for adult patients with dystonia often indicate little improvement. However, these scales may underestimate significant improvements in areas such as pain relief, hand function, and the ability of the child to sit comfortably (Lumsden et al. 2015). These are issues that are of particular concern for patients and their families. At the same time, it must be acknowledged that when a child has DBS there is a strong emotional investment, both from the family and the treating doctors, that it has been a good idea, and assessment of the outcome should be based on hard data and preferably by someone independent of the process. There is a report of patients with CP receiving pallidal DBS who did well with extended follow-up (Romito et al. 2015). Keen et al. (2014) found improvement including in speech, a finding not previously reported, in a small number of children with dystonic CP treated with DBS.

In treating a child with milder forms of dystonia, as is true of all movement disorders, it is always important to not to overlook common comorbidities such as intellectual disability, attention deficit disorder, anxiety and obsessive compulsive disorder. These problems can cause significant impairment and may be more responsive to treatment than the dystonia itself.

**STATUS DYSTONICUS (DYSTONIC STORM)**

Status Dystonicus is a life threatening form of dystonia where complications include severe pain and exhaustion, respiratory failure and metabolic disturbances such as rhabdomyolysis and renal failure. It can be an extremely difficult condition to treat, and there is as yet no satisfactory definition of what constitutes status dystonicus in childhood (Baxter 2013).

Fasano et al. (2012) reviewed 89 episodes of status dystonicus in 68 patients, of whom almost 60% were under the age of 15 years. This is by far the largest review of status dystonicus. The study included 27 of their own patients, and 41 reviewed from the literature. Fasano et al. divided the clinical features into (1) tonic status dystonicus where there were sustained contractions and abnormal postures, and (2) phasic status dystonicus where there were rapid and repetitive dystonic contractions. The tonic subtype was the more common, accounting for two-thirds of the episodes. In one-third of patients there was no clear trigger. When a trigger was evident, it was infection (52%), changes to medication (30%), a surgical procedure (7%), metabolic disorders (5%) and failure of a DBS device (5%). Initial treatment was with medication in most patients, but in only around 10% was the status dystonicus stopped in this fashion, most often by using tetrabenzine and benzhexol. Other treatments included intravenous benzodiazepines, propofol sedation, muscle paralysis, surgery (either DBS or ablations), barbiturate anaesthesia, and intrathecal baclofen. Overall, 10% of patients died, 37% returned to their pre-existing clinical state, 37% improved (some markedly) and 16% were worse than they had been prior to the episode of status dystonicus.

Allen et al. (2014) stress the importance of allowing the child with status dystonicus to sleep to reduce the otherwise unremitting dystonic spasms. They recommend the judicious use of oral or nasogastric chloral hydrate to obtain this. Allen et al. also list features differentiating status dystonicus from similar conditions such as neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia and paroxysmal autonomic instability with dystonia (a condition which can occur after a severe head injury).
To prevent status dystonicus catching hold, it is important to recognize when a child’s dystonia is worsening. For example, patients with dystonia who have surgery need to be watched very carefully, so as they do not slowly slip into status dystonicus. A Dystonia Severity Action Plan has been developed (Lumsden et al. 2013). Allen et al. (2014) incorporate this into a logical flowchart for the management of status dystonicus. They also review surgical approaches including pallidotomy and DBS.

Status dystonicus most often occurs in patients known to have dystonia. Therefore, if life-threatening dystonia develops in a previously well person, (1) underlying genetic and metabolic disease should be sought such as thiamine transporter-2 deficiency (discussed Treatable Movement Disorders section); and (2) other potentially treatable conditions should be considered, such as anti-NMDA receptor antibody encephalitis, where the treatment is primarily with immunosuppression rather than with anti-dystonic agents.

Advances in the management of status dystonicus are likely to come from carefully conducted international trials. However, the most important part of management will always be the recognition that a child with dystonia is worsening, allowing preventive action to be taken. The incidence of status dystonicus with surgical procedures seems too low to recommend routine, peri-operative preventive treatment in children with established dystonia, but this might be considered in some patients.

### ATHETOSIS

The term athetosis was coined by William Hammond in 1871 to describe continuous, slow, writhing movements of the fingers, toes, and face. Subsequently, its use changed to describe what we now call dystonia (Morris et al. 2002a). It is a term that has now gone out of favour, mainly appearing as the hybrid ‘choreoathetosis’ when both fast and slow movements co-exist. Morris et al. (2002b) have suggested the term athetosis should be retained and used in its original sense. It is a distinctive form of dystonia seen with mild CP. Typically there are independent, quivering movements of the face and eyebrows. Similarly irregular, brief, jerky movements occur in the hands and sometimes feet. Sanger et al. (2010) proposed the following definition of athetosis: ‘athetosis is a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture’. They suggested athetosis could be distinguished from dystonia by the lack of sustained postures, ‘although it is frequently associated with dystonia so the distinction can be difficult in practice’.

### CHOREA

The word chorea comes from the Greek _choreia_, a ‘choral dance’, and the concept of a dance remains helpful in its recognition. The characteristic feature of chorea is the flow of movement from one part of the body to the next. As is typical of most movement disorders, variability is the rule. At times chorea can consist of brief sudden twitches similar to tics or myoclonus, and at other times there are longer duration sinuous movements that are called choreoathetosis. The severity of chorea can vary from (1) a child that simply looks restless with a mild intermittent exaggeration of gestures or expressions; (2) to a more obvious chorea with a ‘dancing’ gait; and (3) at the extreme a continuous flow of violent, and totally incapacitating ‘ballistic’ movements.

The essence of chorea is an impression of an unpredictable flow of the movement. Other movement disorders such as dystonia, myoclonus, and tics tend to form patterns, and there is a degree of predictability in the muscles that are involved. Clinically, with chorea there is no such pattern. This can be helpful in differentiating multifocal tics from jerky chorea. Another feature helping to distinguish chorea from multifocal tics, is that chorea disturbs normal motor function, whereas tics usually do not.

Except when it is very severe, children with chorea are able to perform voluntary movements, but cannot control additional, unwanted movements. They may attempt to disguise their unwanted movements. For example, when an arm flies upwards, they will brush their hair, and then keep moving. Chorea typically involves the face. This is reflected in Kinnier Wilson’s dictum that the child with Sydenham chorea is punished three times before the diagnosis is made – ‘once for general fidgetiness, once for breaking the crockery, and once for making faces at grandmother’.

Other manifestations of chorea include motor impersistence. The child is unable to keep their arms extended out in front of them, and the arms repeatedly drop downwards, or flex at the elbow. Other well-known manifestations of motor impersistence include difficulty in keeping the tongue protruded, and difficulty maintaining a steady grip (‘milkmaid’s grip’).

Generalised chorea is often asymmetrical, but when confined to one side of the body, the term hemichorea is used. The cause is often injury to the contralateral basal ganglia. Hemiballismus is generally regarded as an extreme manifestation of chorea. It is characterised by unpredictable, wild, flinging movements, particularly affecting the limbs proximally. While the patient is awake the limb is in constant and violent motion, but with sleep it becomes completely still (Purdon Martin 1927). Hemiballismus is rare in childhood but in adults is classically caused by a lesion of the contralateral STN. Bilateral ballistic movements can be seen in children with a variety of severe encephalopathies.
## Table 19.6  Some causes of chorea

<table>
<thead>
<tr>
<th>Genetic diseases</th>
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<tbody>
<tr>
<td>Huntington disease</td>
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<tr>
<td>NKK2.1 mutations</td>
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<td>ADCY5 mutations</td>
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<tr>
<td>Chorea–acanthocytosis</td>
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<tr>
<td>PDE10 mutations</td>
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<td>GNAO1 mutations</td>
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<tr>
<td>Bilateral infantile striatal necrosis</td>
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<tr>
<td>Wilson disease</td>
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<tr>
<td>Denterorubropallidolysian atrophy</td>
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<td>Ataxia–telangiectasia</td>
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<td>Ataxia–oculomotor apraxia types 1 and 2</td>
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<tr>
<td>Friedreich ataxia</td>
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<td>Lesch–Nyhan disease</td>
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<tr>
<td>Niemann–Pick type C</td>
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<tr>
<td>Atypical nonketotic hyperglycinemia</td>
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<td>Cerebral folate deficiency (FOLR1 mutations)</td>
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<th>Acquired causes</th>
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<tbody>
<tr>
<td>Infectious and inflammatory/autoimmune diseases</td>
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<td>Sydenham chorea</td>
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<td>Systemic lupus erythematosus</td>
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<td>Antiphospholipid syndrome</td>
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<td>Anti-NMDAR encephalitis</td>
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<td>Post herpes simplex encephalitis</td>
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<td>Viral diseases, including HIV</td>
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<td>Multiple sclerosis</td>
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<td>Behçet disease</td>
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<td>Neuroborreliosis (Lyme disease)</td>
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<td>Cyanotic heart disease</td>
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<td>Cardiac surgery with hypothermia (post-pump chorea)</td>
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<td>Haematological diseases (leukaemia, polycythaemia)</td>
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<th>Intoxications</th>
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<td>Phenytoin</td>
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<td>Amphetamines, methylphenidate abuse</td>
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<td>L-dopa (if this occurs at low doses, it raises the possibility of an inborn error of dopamine metabolism)</td>
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<td>Other organic acidurias</td>
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<td>Homocystinuria</td>
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<td>Mitochondrial disorders</td>
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<td>Dihydropteridine deficiency</td>
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<td>Sulphite oxidase deficiency</td>
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<td>Creatine deficiency</td>
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<td>Phenylketonuria</td>
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<td>Gangliosidosis types I and II</td>
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<td>Chronic subdural haematoma</td>
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<td>Hyper/hypoglycaemia</td>
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<td>Central pontine myelinosis</td>
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<td>Sequela to status epilepticus</td>
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<td>Infantile chorea secondary to bronchopulmonary dysplasia</td>
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NMDAR, N-methyl-D-aspartate receptor; HIV, human immunodeficiency virus.

In Table 19.6 we list some of the large number of potential causes of chorea. In the following discussion, we will concentrate on a limited number of important causes of chorea.

### SYDENHAM CHOREA

Sydenham chorea was the first form of chorea to be described and the first movement disorder to be recognised as immune-mediated. It is a consequence of a group A β-haemolytic streptococcal infection. It usually occurs between the ages of 5 and 15 years, and girls are more commonly affected.

The clinical manifestations of Sydenham chorea include the classic features of chorea described above. In mild cases the child may just appear restless. Dysarthric, explosive speech, combined with chewing and swallowing difficulties, may occur in the more severe cases. Attempts at movement tend to make the chorea worse, but some children can integrate the chorea into normal movements lessening their impact. There may be irritability, emotional lability and the development of obsessive–compulsive symptoms (Swedo et al. 1993). Asymmetry of chorea is common. Although some authorities believe an isolated hemichorea may occur in Sydenham chorea (Ford 1960), Sheldon (1940) was of the view that...
reports dramatic emotional changes. From Sheldon’s textbook
‘The mental symptoms may persist for a long time and,
overshadowed by the motor symptoms. Ford (1960)
long been recognised with Sydenham chorea, it has tended to be
the most effective drug in the treatment of Sydenham chorea.
haloperidol were changed over to valproate and within a week
and another a dystonic reaction. Four patients treated with
lowing 5 days of treatment, but one had excessive somnolence,
patients treated with haloperidol showed improvement fol-
No side effects were noted with either drug. Three of the six
ance of symptoms. The remaining patient failed to improve.
Three recovered after 5 days of treatment, whereas the other
casual heart disease in children with Sydenham chorea. In the classic paper
of Aron et al. (1965), 34% of 50 patients examined an average
of 29 years after their initial episode, had developed valvu-
lar heart disease. In a more recent study of Sydenham chorea
from Turkey, using echocardiography, carditis was detected in
71% of 69 children at initial presentation (Ekici et al. 2012).
The carditis was silent in 28.9%. In this study, most patients
had mild or moderate valvular regurgitation.
Patients who have had rheumatic carditis, with or with-
out valvular disease, are at a relatively high risk for recurrences
of carditis. They are likely to sustain increasingly severe cardiac damage with each episode. Therefore, it has been recommended that patients who have had rheumatic carditis should receive long-term antibiotic prophylaxis well into adulthood (Gerber et al. 2009). If there is valvular heart disease the prophylaxis may need to be life-long. In deci-
ding the duration of the prophylaxis, it is important to assess
the likelihood of ongoing exposure to group A β-haemolytic streptococcal infection. Prophylaxis usually takes the form of
intramuscular benzylpenicillin every 28 days, or oral penicil-
in 250mg b.d., unless the person has penicillin allergy, where
sulfadiazine or macrolide antibiotics can be used (Gerber et al. 2009). It should be remembered that penicillin prophylaxis is
to prevent further episodes of carditis. It may not prevent
relapses of chorea which can occur in up to 20% of patients.
The relapses appear to be unrelated to repeated streptococcal infections (Ekici et al. 2012), but may be triggered by other
infections, the oral contraceptive pill or pregnancy.

THE SYNDROME OF BENIGN HEREDITARY CHOREA

An autosomal dominant non-progressive form of chorea without intellectual deficit was described in 1967 (Haerer
et al. 1967; Pincus and Chutorian 1967). At one point, doubt
was cast as to the existence of this condition (Schrag et al.
2000). However, genetic studies then revealed that mutations
in the gene NXX2.1 (also known as TITF1) was responsible
for some cases (Devriendt et al. 1998; Breedveld et al. 2002).
Recently other genes have been described with clinical mani-
festations that broadly fit into the spectrum of benign heredi-
tary chorea (BHC).
**NKX2.1/TITF1 Mutations**

The *NKX2.1* gene encodes a transcription factor that is expressed early in the development of the basal ganglia, hypothalamus, thyroid and lungs (Thorwarth et al. 2014). With mutations in this gene, as well as chorea there may be hypothyroidism and lung disease. There is a female predominance, and the first signs are often hypotonia and motor delay, with the median age at onset of chorea being 3 years of age (Peall et al. 2014). There may be no lung or thyroid disease, or the manifestations may be subtle with a mildly elevated thyroid stimulating hormone (TSH), but otherwise normal thyroid function tests. The lung disease when present, has a wide spectrum from neonatal respiratory failure, through recurrent chest infections and asthma, to lung cancer in adults (Gras et al. 2012). Confusing for the clinician, but not surprising when considering the function of *NKX2.1*, there may be other movement disorders such as dystonia, myoclonus and tics (Asmus et al. 2007b; Gras et al. 2012).

There are a number of reports of children with *NKX2.1* mutations initially presenting with frequent falls, with chorea appearing subsequently (Fons et al. 2012; Rosati et al. 2014). If the contiguous gene *PAX9* is deleted there may also be poor development of the teeth (Devos et al. 2006).

Gras et al. (2012) found that the chorea improved after puberty, and occasionally myoclonus becomes the most disabling problem in adults. They also found a relatively high incidence of learning difficulties and attention deficit disorder. Short stature and cardiac defects have also been reported, and as discussed above, mutations in the *NKX2.1* gene may predispose to the subsequent development of malignancies (Thorwarth et al. 2014). In some patients, MRI reveals a cystic pituitary mass (Veneziano et al. 2014).

There is limited information about the treatment of the movement disorders that can appear in *NKX2.1* gene mutations. Peall and Kurian (2015) in a recent review observed: ‘Multiple reports have described single cases treated with a variety of agents including trihexyphenidyl, corticosteroids, sodium valproate, propranolol, ropinirole, and sulpiride, each with varying results.’ There are reports of patients with *NKX2.1* mutations responding to L-dopa therapy. Asmus et al. (2005), described two patients who showed improvement of gait and chorea with L-dopa, using relatively high doses of 20mg/kg/day. In one of these patients, increasing the dose to 33mg/kg/day led to worsening of gait, and a return to the lower dose. CSF pterins, measured in one of the patients were normal. Fons et al. (2012) using a dose of 9mg/kg/day of L-dopa, given from 3.5 years of age, with a very slow titration, found that after 6 months of treatment including physiotherapy, there was a significant improvement in neurological symptoms. After a year there was an attempt to stop the L-dopa, but this resulted in a deterioration in gait and frequent falls. The patient continued on a lower dose of 3mg/kg/day for a further 14 months. The L-dopa was then stopped after a total of 3 years of treatment, without any clinical deterioration. A detailed analysis of this patient’s CSF neurotransmitters did not reveal any abnormalities, suggesting that there was no lack of production of L-dopa.

In the study of Gras et al. (2012), eight patients with *NKX2.1* mutations (children and adults), were given tetrahydronorsergic for their chorea, and five rapidly showed a moderate to marked benefit. However, three stopped the drug within days because of side effects.

**Adenylyl Cyclase 5 (ADCY5) Mutations**

The original family with this condition was described as having ‘familial essential (‘benign’) chorea’ (Bird et al. 1976). Subsequently the diagnosis was changed to ‘familial dyskinesia and facial myokymia’ because of distinctive facial movements that in some members of the family were thought to be myokymic (Fernandez et al. 2001). Subsequently, mutations in the *ADCY5* gene were found to be the cause of the movement disorder in this family (Chen et al. 2012). A re-analysis of the facial movements has concluded that the movements are not myokymic, but due to either chorea or dystonia (Chen et al. 2015). Recent reports have described patients with isolated chorea and dystonia without facial myokymia (Carapito et al. 2015; Chen et al. 2015; Mencacci et al. 2015b). Both familial and sporadic cases have been described. It appears likely there will be a broad spectrum of manifestations of *ADCY5* mutations, from severely affected patients, often carrying the label of dyskinetic CP through to older children where the clinical picture is somewhere between benign hereditary chorea and myoclonus dystonia (Chang et al. 2016).

Chen et al. (2015) have listed the following clues to the diagnosis of *ADCY5* mutations: (1) axial hypotonia, sometimes accompanied by weakness; (2) facial chorea or dystonia; (3) nocturnal paroxysmal dyskinesia, often pronounced; (4) movement related pain; (5) dramatic fluctuations in frequency and severity of movements; (6) no or mild cognitive impairment; (7) normal MRI; and (8) little or no progression. They have suggested the term ‘ADCY5 dyskinesia’ be used in view of the broad range of clinical manifestations and the multiple movement disorders that can be seen associated with the various mutations.

Assessment of the response to medication can be difficult, as some patients follow a waxing and waning course. Benzodiazepines may help the severe nocturnal episodes of dyskinesia that can last hours, and prevent sleep. Three patients treated with DBS before their *ADCY5* mutations were identified showed some improvement in their dyskinesias (Dy et al. 2016). Although there are a wide range of manifestations, ADY5 mutations should be particularly considered in children carrying the label of dyskinetic CP especially when there are unusual facial movements, or bouts of prolonged dyskinesia during drowsiness.

**Clinical Overlap of NKX2.1, Epsilon Sarcoglycan and ADCY5 Mutations**

In the young child who has a hyperkinetic movement disorder, it is often difficult to be certain whether the movements should
be called chorea, dystonia or myoclonus, and at times they co-exist. If neuroimaging is normal, and the child is not severely delayed, then mutations in \( \text{NKX}2.1 \), \( \text{ADcy5} \) and epsilon sarcoglycan mutations come into the differential diagnosis. Abnormal thyroid function tests, including an isolated raised TSH, suggest the diagnosis of \( \text{NKX}2.1 \) mutations in this setting.

**OTHER GENETIC CAUSES OF CHOREA**

Allan-Herndon-Dudley syndrome (AHDS) is an X-linked disorder due to mutations in the \( \text{SLC16A2} \) gene encoding the monocarboxylate transporter 8 (MCT8) (Dumitrescu et al. 2004). Affected patients have early-onset hypotonia, and there may also be dystonic posturing of the limbs, as well as paroxysmal dyskinesias (Brockmann et al. 2005; Gika et al. 2010). In AHDS, there are characteristic abnormalities of thyroid function tests including high free or total \( \text{T}3 \), normal or mildly decreased free thyroxine, and normal or slightly elevated thyroid stimulating hormone. As \( \text{T}3 \) levels are not routinely measured by most laboratories, in males it could be confusing with mutations in \( \text{NKX}2.1 \). However, in AHDS, there is usually severe intellectual disability (Brockmann et al. 2005). There may also be facial dysmorphic features, and MRI shows delayed myelination which can be of such severity that the diagnosis of Pelizaeus–Merzbacher syndrome comes into consideration (Gika et al. 2010).

\( \text{PDE10} \) mutations can cause a relatively benign form of chorea with onset in childhood (Mencacci et al. 2016). A distinguishing feature from other conditions carrying the ‘BHC’ phenotype, is the presence of bilateral abnormalities of the caudate and putamen on MRI.

Mutations in \( \text{GNAO1} \), in contrast, can produce a very severe hyperkinetic movement disorder, usually on a background of hypotonia and developmental delay, with normal MRI (Ananth et al. 2016; Kulkarni et al. 2016). Hyperkinetic status is a feature and is precipitated by multiple factors including infections, excitement, anxiety and emotional stress. There are frequent admissions to the Intensive Care Unit, and the child may die despite maximum medical therapy. DBS shows promise in controlling the bouts of hyperkinetic status (Kulkarni et al. 2016).

**CHOREOATHETOSIS FOLLOWING HERPES SIMPLEX VIRUS ENCEPHALITIS**

In 1967 in a review article, Olson et al. described a 70% mortality rate for herpes simplex virus encephalitis (HSE) (Olson et al. 1967). In 1973, adenosine arabinoside was introduced and was the first effective treatment for HSE. Acyclovir was introduced in 1982 and has become the treatment of choice, reducing mortality to between 0 and 25% (Whiteley et al. 1986).

Soon after the development of effective therapy, ‘relapses’ following treatment of HSE were reported. In 1979, Koenig et al. reported an adult patient who developed ‘post infectious encephalomyelitis’ after treatment with adenosine arabinoside for HSE. In the 1980s and 1990s multiple papers were published describing relapses after HSE. It became clear that these involved two different populations. In one group there was a reactivation of the herpes virus. In the other, the process was immune-mediated. De Tiège et al. (2005) described the typical features of the immune-mediated form. These included (1) choreoathetoid movements; (2) absence of new destructive changes on imaging; (3) absence of efficacy of acyclovir; (4) diffuse white matter involvement in some cases (see Fig. 19.12); and (5) absence of virus isolation from brain biopsies.

Pruss et al. (2012) looked at the serum of 44 adult patients who were PCR-positive for herpes simplex virus. One-third were found to have antibodies to the NMDA receptor. Subsequent papers (Armande et al. 2013; Hachen et al. 2014; Mohammad et al. 2014a) have established that anti-N-methyl-D-aspartate receptor (NMDAR) antibodies are found in children who develop the syndrome of choreoathetosis following HSE. It seems likely that the mechanism is lysis of infected neurons releasing antigens, leading to a secondary immunological insult (Titulaer et al. 2014).

It has long been recognised that an immune-mediated encephalitis can follow infections such as measles and varicella, where the brain was not initially involved. With HSE, a destructive encephalitis seems to provoke a secondary immune-mediated encephalitis. There may be a role for aggressive immunotherapy in these children. Armande et al. (2013) treated their patient with intravenous methylprednisolone and immunoglobulin, but she did not respond well. Four months after onset, as there had been no improvement, rituximab and cyclophosphamide were added with benefit. It may be difficult to assess the efficacy of aggressive therapy in this condition. It is rare, and there is a variable degree of initial destruction by the herpes virus itself, and presumably a variable immune response, given that the diffuse white matter changes are seen only in some patients.

**HUNTINGTON DISEASE**

Huntington disease is dominantly inherited and characterised by movement disorders, psychiatric disturbance and progressive dementia. It is caused by an unstable, expanded CAG triplet repeat in the \( \text{IT15} \) gene producing an enlarged polyglutamine stretch in the huntingtin protein (The Huntington’s Disease Collaborative Research Group 1993; Schiefer et al. 2015). In Huntington disease, the number of repeats markedly influences the onset and course of the disease (Andresen et al. 2007; Langbehn et al. 2010). Normal individuals have less than 26 CAG repeats. If there are between 27 and 35 repeats the person will not develop symptoms, but could pass the disease on to their children. With 36–39 repeats there is a risk the person will develop the disease, and there is a 50% risk of transmission to their children. If there are 40 or more repeats, the person will develop the disease and there is again a 50% risk of transmission to their children. Anticipation (progressively earlier appearance
of the disease with successive generations) is a feature of Huntington disease, and is more common when the father is affected.

Huntington disease is traditionally subdivided into adult and juvenile-onset forms (where the onset is less than 20 years of age) (Koutsis et al. 2013). In adult onset disease, chorea is often the dominant movement disorder, but rather than being similar to the large amplitude, flowing movements seen in Sydenham chorea, it takes the form of jerky, non-repetitive and arrhythmic movements that affect the facial muscles, fingers and toes (Schiefer et al. 2015). These movements may be misinterpreted as agitation or nervousness, and the affected person is often initially unaware of their presence. In the juvenile form, the traditional view is that rigidity is the most typical early manifestation (known as the Westphal variant).

**Huntington Disease Presenting at Less Than 10 Years of Age**

It is more useful to subdivide juvenile Huntington disease into children with onset before 10 years of age, and those with an onset between 10 and 20 years. Osborne et al. (1982) described three cases of Huntington disease presenting at less than 10 years of age, and reviewed 43 other cases from the literature (acknowledging the limitations of such a study). Of the 46 patients with onset less than 10 years of age, 26 were clearly identified as having the rigid variant, and nine predominantly had chorea. Seizures were reported in 24 children, and they were mainly tonic-clonic seizures, which became more difficult to control as the disease progressed. In one family, seizures were the presenting symptom. Speech disorders were common appearing in 33 of the 46 patients.

Gonzalez-Alegre and Afifi (2006) looked at 12 children affected with Huntington disease. At the time of onset of their symptoms, seven children were under the age of 10 years, with six of them aged between 4 and 5 years. The onset of symptoms in the other five children was between 10 and 14 years. Seizures only appeared in the children with onset at less than 10 years of age. Orpharyngeal dysfunction was common in both groups, but present in all the older children. Chorea was more common in the younger group, whereas rigidity was more a feature of the older group. Two patients in the younger group developed paroxysmal dystonia initially affecting the right arm when walking or running. This subsequently became generalised and almost continuous. The most frequent presenting symptom of the earlier onset group in this study was cognitive decline. Two of the patients were initially diagnosed by a child psychiatrist as having attention-deficit–hyperactivity disorder (ADHD), and another had frequent motor tics. In four children (three in the under-10 group), the initial CT or MRI was normal. Caudate atrophy was found in the other scans, sometimes with more diffuse atrophic changes. Although juvenile Huntington disease is traditionally associated with paternal inheritance, the affected parent was the mother in three of the seven children presenting at under 10 years of age. One of these children had 120 CAG repeats. None of the 12 patients had the abnormalities of eye movements that are frequently seen in adult patients with Huntington disease.

Looking at their own patients and previous reports, Gonzalez-Alegre and Afifi (2006) felt that childhood-onset Huntington disease could be seen in three phases: (1) an initial phase of behavioural disorder, learning difficulty, gait disturbance and mild chorea; (2) a florid phase with signs of cognitive deterioration, rigidity, speech disturbance and seizures; and (3) a terminal phase of bed confinement, hypotonia, and increasing seizures.

**Huntington Disease Presenting after 10 Years of Age**

Ribaï et al. (2007) described 29 patients with juvenile Huntington disease. The mean age at onset was 14 years with a standard deviation of 5 years, and almost half had less than 60 repeats. They thus represented the ‘older’ group of juvenile Huntington disease. The initial problem was motor in ten patients, cognitive in ten patients, and in nine, it was psychiatric disturbance. Overall, psychiatric and behavioural difficulties were severe enough to be reported as the first sign by patients and relatives in 66% of patients. Seven patients attempted suicide at least once. Cognitive decline ranged from slight attentional difficulties to subcortical dementia. At onset the motor signs were atypical, including ‘myoclonic head or limb tremor’, shoulder twitching and writing difficulties. Only three had chorea at the onset of the illness. None of the patients were initially rigid, but during the course of the disease, parkinsonism was present in 62%, and dystonia in 72%. Over time, chorea appeared in 62%, cerebellar signs in 24% and seizures in 21% of patients. When the patients presented with behavioural or psychiatric disturbance, even with a known family history of Huntington disease, diagnosis was often delayed. In one case, the carrier father remained asymptomatic at 69 years of age. Ribaï et al. (2007) suggested that Huntington disease be considered in a child or young adult with an atypical movement disorder, combined with severe, progressive psychiatric or cognitive disturbances, even in the absence of family history of Huntington disease.

Delayed speech or severe dysarthria can be an important clue to the diagnosis of childhood Huntington disease. As well as the above studies, this was found in 18 out of 20 patients in the review of Hansotia et al. (1968). Yoon et al. (2006) described three patients with Huntington disease where speech delay preceded motor symptoms by 2 years. Ataxia was a feature of 50% of the children in the study of Hansotia et al., and was also noted by Ruocco et al. (2006). In a multicentre review of 90 patients with juvenile Huntington disease, seizures occurred in 38% and were more likely to occur with earlier age at onset and greater expansion size (Cloud et al. 2012). There is a report of Huntington disease presenting as a progressive myoclonic epilepsy (Gambardella et al. 2001).

The issue of when to test for Huntington disease is difficult. Koutsis et al. (2013) reviewed the notes of 76 patients...
Chapter 19 Basal Ganglia Diseases and Movement Disorders

suspected of having juvenile the disease. All of the 24 patients who carried the Huntington disease expansion, had a positive family history of Huntington disease. Overall, 23% of patients with a family history of genetically confirmed Huntington disease, did not have an expansion. Clinical symptoms were not reliable in predicting who would carry the abnormal gene. Koutsis et al. concluded that in the absence of a family history, the diagnosis of Huntington disease was unlikely, and there should be no delay in performing investigations to look for other causes.

In an accompanying editorial Lehman and Nance (2013) discussed the challenge of the 10–20-year-old patient, with a family history of Huntington disease, presenting with symptoms common at that age such as depression, anxiety, and behavioural, cognitive or attention problems. They suggested that to avoid both delayed diagnosis, and either a premature or incorrect attribution of symptoms to the disease, a period of observation of around 1 year should be undertaken. If over this time a clearly progressive course was established, then testing could reasonably be done. Some authorities take the view that under the age of 18 years, testing should not be done. The reasons are discussed by Lehman and Nance (2013), and in multiple other reviews.

There is as yet no effective treatment for Huntington disease, and therapy for juvenile Huntington disease tends to be symptomatic, and aimed at reducing patient and family distress. In a survey of 45 patients with juvenile the disease from Europe and the United Kingdom, 24 were receiving antipsychotic agents, 17 anti-depressants, 15 anti-parkinsonian medications and eight valproic acid for seizures. Reflecting the difficulty of management, polytherapy was common, with five patients taking more than eight medications, and one patient received 16 different medications. In the United Kingdom opioids were also used for pain relief.

**TREMOR**

Tremor particularly affects the upper limbs but can involve almost any part of the body including the head, face, eyelids, tongue, vocal cords and trunk. In a Consensus Statement of the Movement Disorders Society, tremor was defined as ‘a rhythmic, involuntary, oscillatory movement of a body part’ (Deuschl et al. 1998). There is a paucity of data on the prevalence of tremor in childhood, but in the personal series of Fernández-Alvarez of children under 18 years with movement disorders, 129 (19%) of 673 cases presented with tremor as the sole or predominant feature. It was seen twice as commonly in boys, and the apparent age at onset was typically around 6 years (Fernández-Alvarez and Aicardi 2001).

While taking the history, watching how the child manipulates toys, or plays a computer game can give useful information. There are a number of ways of formally assessing a child for tremor. These include asking the child to hold their arms out in front, and then getting them to do mental arithmetic (at a level that challenges them). With mental arithmetic, a pathological tremor often becomes worse, whereas it may disappear if the problem is psychogenic. Other useful techniques include with the arms abducted getting the child to keep both index fingers as close as possible to the nose without touching it, and copying an Archimedes spiral.

Tremor is traditionally divided into resting tremor and action tremor. Using tremor of the upper limbs as an example, with resting tremor, the tremor is seen when the arm is totally relaxed. Full relaxation is not always easy to achieve, but asking the child to rest the arm on the bed and let it become ‘loose’ may be effective. Action tremor is any tremor that is produced by voluntary contraction of muscle. It is further subdivided into (1) postural tremor which occurs when a limb is voluntarily maintained against gravity for example, when the arms are held steadily straight out in front of the child, and (2) kinetic tremor defined as any tremor that occurs during voluntary movement.

Kinetic tremors can in turn be subdivided. Intention tremor worsens as a target is approached, classically in the ‘finger-nose’ test. Simple kinetic tremor occurs during voluntary movements that are not goal-directed for example, during pronation/supination movements of the forearm. Task specific tremors occur during, or are provoked by, a particular action; for example, writing. Titubation is the slow head tremor typically seen with cerebellar disease, but also in adults with essential tremor. The head movements can be in an anterior-posterior or lateral direction. Holmes tremor is present at rest, with intention, and with posture. It is typically slow and coarse. It can be extremely disabling. In Holmes tremor, with the finger-nose test, as the hand returns to the nose there may be extreme oscillations of the hand, and the threat of injury to the eyes or face. The term Holmes tremor is now preferred to such terms as rubral or midbrain tremor which were used in the past. It is believed to be caused by involvement of both the nigrostriatal and dentato-rubro-thalamic pathways (Deuschl et al. 1998).

Children with irregular jerking movements of the hands or arms are often described as having dystonic tremor. This can be confusing as the movements are often neither rhythmic nor oscillatory, features that are generally regarded as mandatory in the diagnosis of tremor. If the person has other signs of dystonia, then the diagnosis is not difficult. However, a common presentation is the child who has mild, intermittent, irregular
jerking of the hands, but is otherwise normal, and all investigations are negative. This possibly represents a mild form of dystonic tremor.

Tremor studies can be done relatively easily in children but the diagnosis is usually made on clinical grounds. Singer et al. (2010) observed: ‘Electromyography, accelerometers, and other instruments are sometimes used to quantitate tremors, but the clinical utility of this information, that is, its ability to improve diagnostic and/or therapeutic medical decision making, has not been demonstrated in children.’ However, Canavese et al. (2008), in a retrospective review of 61 children who had a tremor study, found that in 31% the polygraphic features allowed the identification of a clinically unclassified movement disorder. Further, in 19.6% it disclosed an associated movement disorder which was not clinically evident. It was also useful in supporting the clinical diagnosis of psychogenic movement disorder.

At present, tremor studies can be seen as a useful adjunct that may help to confirm the clinical impression. When the child has a psychogenic movement disorder, tremor studies also can be helpful in persuading the parents and child that there is ‘scientific’ evidence supporting the diagnosis.

‘JITTERINESS’

As many as half of all term infants are jittery and as such, this is the most common form of tremor in childhood. It usually settles over a few days, but in some infants persists for months. Asphyxiated infants may show it in an extreme form. In jitteriness high-frequency, rhythmic oscillatory movements, particularly of the limbs and chin, can be provoked by startle, and be stopped by gently holding the moving limb, or changing its position. The main differential is a clonic seizure where the limb jerking will usually continue despite gentle restraint or repositioning. A fundamental difference is that the ‘to and fro’ movements of jitteriness are of equal amplitude, whereas in clonic seizures, the phase of flexion is usually more sustained than that of extension (Scher 1997).

TREMOR IN INFANCY

There are a relatively small number of causes of tremor in infancy (see also Table 19.14).

Inborn Errors of Dopamine Metabolism

These are rare and the infant may be misdiagnosed as having the much more common CP. This subject will be discussed in more detail in the Parkinsonism section.

Cobalamin (Vitamin B12) Deficiency

In 1962, Jadhav reported the syndrome of vitamin B12 deficiency in Indian infants characterised by apathy, developmental regression, involuntary movements and skin pigmentation. Subsequently there have been multiple similar reports from the ‘developed’ world. The typical story is that the mother has vitamin B12 deficiency due either to her diet, or undiagnosed pernicious anaemia. The infant is exclusively breastfed. From around 4–8 months there is progressive developmental regression. The infant may not be anaemic, but the blood film is often macrocytic. The movement disorder can be present before diagnosis, but is more often seen after treatment with vitamin B12 has started. It is commonly described as ‘choreoathetosis’ (Graham et al. 1992), but in some children the movement disorder is more rhythmic (Higginbottom et al. 1978). At times it takes the form of a violent tremor that can cause the cot to shake (Emery et al. 1997). In a series of three patients, two had pronounced limb shaking thought to be a mixture of tremor and myoclonus (Gratton-Smith et al. 1997). One of these infants also had marked jerking of the tongue and pharynx causing vocalisation. The third infant had persistent movements of the right hand resembling epilepsy partialis continua, which appeared before treatment was started.

Both seizures and movement disorders can occur in vitamin B12 deficiency, and it is important to try to separate the two. The violent tremor that appears after the initiation of treatment usually settles over 4–6 weeks. Why it occurs is not known.

In the developing world, the ‘kwashiorkor shakes’ has been described in severely malnourished children on re-feeding (Kahn and Falcke 1956). Again the cause is unknown.

Head Tremors in Infancy

Head tremor at all ages can be further subdivided into ‘negative’, when the head shakes from side to side; and ‘positive’ (or affirmative) when the shaking takes the form of a vertical nodding. Some children with congenital nystagmus have head shaking movements. It is not clear why these head movements occur, but there are usually no diagnostic difficulties when shaking occurs in the presence of coarse, horizontal, pendular nystagmus. Totally blind children may also have repetitive head movements that may be a form of self-stimulation (Fazzi et al. 1999). The term ‘bobble-head doll syndrome’ (BHS) was introduced by Benton et al. (1966) and subsequent reports have not improved upon their description. Two children were described with ‘to and fro’ bobbing or nodding of the head and trunk. ‘The movement is reminiscent of that seen in dolls with weighted heads resting on a coiled spring’. Both children had cysts in relation to the third ventricle with associated hydrocephalus. Subsequent reports have confirmed that BHS is typically caused by mass lesions around the third ventricle causing CSF obstruction.

Nellhaus (1983) lists hypomagnesemia, uremia, thyrotoxicosis, citrullinaemia, antihistamines, antipsychotic agents and amphetamine as other causes of head tremor in childhood.

In spasmus nutans there is asymmetrical, rapid head nodding, nystagmus (often monocular) and head tilt or torticollis. The nystagmus and head shaking typically occur in bursts.
lasting 5–30 seconds in association with fixation. Classically
described as a benign phenomenon, at times it is caused by an
anterior visual pathway glioma (Antony et al. 1980).

Head Stereotypies in Infancy
Some infants and young children have intermittent, rhyth-
mic, side to side head movements that can persist for years
with no other signs present. Sometimes these will be more
obvious when the child is otherwise unoccupied, and the
movements may disappear with intense concentration, or
if the child is asked to stop the movement. However, this
is not always the case. This appears to be an unusual form
of stereotypy. Hottinger-Blanc et al. (2002) described eight
children with onset in the first year of life of an isolated
head stereotypy. All were of normal intelligence but were
clumsy, and two had abnormalities of cerebellar develop-
dent. Di Mario (2000) described four children with per-
sistent head tremor with no cause identified. Three of these
four children had shuddering attacks (also thought by some
to be a form of stereotypy) prior to the development of the
head movements.

Because of the many potentially serious underlying causes,
neuroimaging should always be considered in children with
head tremors.

TREMORS IN CHILDHOOD AND BEYOND
A common situation is the child thought to have a tremor at
home or school, but when examined, there is either nothing
to see, or there are intermittent, subtle and not uncommonly
irregular, finger movements. Investigations such as thyroid
function tests, copper and caeruloplasmin, a urine metabolic
screen and neuroimaging are normal. Whether this represents
enhanced physiological tremor, the earliest presentation of
essential tremor, or a mild form of dystonic tremor without
other signs present. Sometimes these will be more
obvious when the child is otherwise unoccupied, and the
movements may disappear with intense concentration, or
if the child is asked to stop the movement. However, this
is not always the case. This appears to be an unusual form
of stereotypy. Hottinger-Blanc et al. (2002) described eight
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head movements.

Because of the many potentially serious underlying causes,
neuroimaging should always be considered in children with
head tremors.

ENHANCED PHYSIOLOGICAL TREMOR
All of us have a tremor which is usually only seen under
conditions of stress, such as extreme fatigue, anxiety or after
vigorous exercise. This is physiological tremor, an action
tremor that takes the form of an oscillation of the outstretched
hands at a frequency of 8–12Hz. Probably the commonest
example of enhanced physiological tremor in childhood, is the
child with severe asthma receiving intensive bronchodilator
therapy. Other causes include thyrotoxicosis, hypoglycaemia,
withdrawal syndromes and phaeochromocytomas. In a
review of 110 cases of acquired thyrotoxic tremor identified over
a 1-year period in the United Kingdom and Ireland, tremor
was identified in 58% of children, and was the second most
common sign, with only goiter (78%) being more common
(Williamson and Greene 2010). No details of the nature of
the tremor were provided. Fernández-Alvarez and Aicardi
(2001) have seen children with intellectual disability, whose
exaggerated physiological tremor was so intense in stressful
situations, that the tremor seemed more disabling than the
intellectual problems.

ESSENTIAL TREMOR
Essential tremor is typically a bilateral, largely symmetri-
cal, postural or kinetic tremor, involving mainly the arms
(Deuschl et al. 1998). The head and voice may also be
involved. There is a paucity of literature on essential tremor
in children, especially under the age of 10 years. Reflecting
this, the authors have rarely made the diagnosis with con-
fidence in a young child. Essential tremor was once seen
as a straightforward diagnosis in adults, but despite the
frequency of the diagnosis, and its apparently dominant
inheritance, genetic studies have failed to identify a single
causative gene. It seems likely to that essential tremor will
be found to be a family of diseases, with some patients hav-
ing underlying cerebellar dysfunction, and others a neuro-
derenerative process (Elbe and Deuschl 2011; Grimaldi and
Manto 2013).

A number of conditions can produce a tremor that may be
mistaken for essential tremor including hydrocephalus,
hereditary and motor sensory neuropathies, Wilson disease
and Klinefelter syndrome (Fernández-Alvarez and Aicardi
2001). Hyperthyroidism should also be considered.

PALATAL TREMOR
Palatal tremor was previously called palatal myoclonus, and
is classified into symptomatic and essential forms (Deuschl
et al. 1994). Symptomatic palatal tremor is usually seen in
adults, and results from a stroke or other lesion involving the
dentato-olivary pathway including polymerase-γ (POLG)
mutations (Mongin et al. 2016). There may be hypertrophy
of the inferior olivary nucleus which can be demonstrated on
MRI. The palatal movement is produced by contraction of
levator veli palatini. There may be widespread jerks involv-
ing muscles of many areas, including the face and diaphragm.
These are synchronous with the palatal movements. There are
no ear clicks.

In essential palatal tremor, the movements result from
contraction of tensor veli palatini. Ear clicks are commonly
present, and the movements are restricted to the palate.
There are no abnormalities of the inferior olivary nucleus.
Campistol-Plana et al. (2006) reported four children with a
mean age of 6 years with essential palatal tremor, and found
there was a good response to piracetam. In some cases, essential
palatal tremor appears to be a psychogenic disorder. Stamelou
et al. (2012a) reappraised ten patients with isolated palatal
tremor, and concluded that in seven of them, the problem
was, in fact, psychogenic.
TREMOR IN SPINAL MUSCULAR ATROPHY AND NEUROPATHIES

Moosa and Dubowitz (1973) emphasised the diagnostic value of the presence of a tremor in children with what we now call types II and III spinal muscular atrophy (SMA). They found limb tremor to be more common than fasciculations of the tongue, a better known sign of SMA. The tremor was an action tremor present with outstretched hands, or noted during the manipulation of toys. Similar movements can also be seen in children with congenital neuropathies (Yiu et al. 2011) and in chronic inflammatory demyelinating neuropathy (Ouvrier et al. 1999). The movements are due to the firing of large motor units in muscles with chronic denervation and reinnervation (Riggs et al. 1983). They are not entirely rhythmic and terms such as ‘contraction fasciculations’ (Denny-Brown and Pennybaker 1938) have been used. Spiro (1970) describing children with SMA, called these movements ‘minipolymyoclonus’ a term coined by his colleague Dennis Giblin, and now confusing as it was subsequently used in the setting of epileptic myoclonus (Wilkins et al. 1985). Riggs suggested ‘contraction pseudotremor of chronic denervation’ might be the best term (Riggs et al. 1983).

OTHER DISEASES WITH TREMOR

Tremor is a common symptom of Wilson disease. In his original description Wilson noted: ‘In all my own cases tremor was one of the earliest symptoms, as it was one of the most marked’ (Wilson 1912). The wide range of manifestations of Wilson disease will be discussed in the Treatable Movement Disorders section.

Glucose transporter deficiency can cause a dystonic tremor. It will also be discussed in the Treatable Movement Disorders section.

CONDITIONS THAT CAN IMITATE TREMOR

In epilepsy partialis continua (EPC) there is continuous focal jerking of a body part, usually localised to a distal limb, occurring over hours, days or even years (Cockerell et al. 1996). Sometimes it ceases in sleep. Usually there is sufficient variability in timing and amplitude for the movements to be recognised as not a tremor, but there is a report in the adult literature of a man with EPC initially felt to have a parkinsonian tremor (Al-Hayk and LeDoux 2003). There are many causes of EPC, but if it is due to a focal cortical dysplasia there may be jerking that is localised, and no alteration of consciousness, causing potential diagnostic difficulty. Other causes include Rasmussen syndrome, viral encephalitis (including subacute measles encephalitis) and POLG1 mutations (Cardenas and Amato 2010). In these conditions, there is usually alteration of consciousness and intense seizure activity, taking the diagnosis away from tremor as a possibility.

Familial cortical myoclonic tremor with epilepsy (FCMTE) is a rare disorder which can be mistaken for essential tremor (Van Rootselaar et al. 2005; Licchetta et al. 2013). It is more common in adults, but the onset can be as early as 10 years of age. Typically, there is no tremor at rest but the tremor appears with posture and movement. The ‘tremor’ is actually the result of high-frequency myoclonic jerks of cortical origin. In the video of a case shown by Van Rootselaar, the jerking was mainly present in the fingers and hands. It was high-frequency, semi-rhythmic and of varying amplitude. It was stimulus sensitive and neurophysiology was consistent with a cortical reflex myoclonus. The inheritance of FCMTE is autosomal dominant. At the time of writing, the genetic abnormality has not been identified. Tremor is usually the first symptom, with epilepsy developing over time, typically generalised tonic-clonic seizures or prolonged myoclonic seizures.

Hereditary geniospasm (literally ‘chin spasm’) or chin quivering is a highly distinctive disorder involving the mentalis muscle of the chin. Typically, there is an ‘up and down’ movement of the chin with quivering of the lip. The movements do not have the rhythmicity of tremor, rather they come in irregular bursts. They tend to be worse with anxiety. The movements can be quite strong and may give the impression that they emanate from the jaw. If there is significant social disability from the movements, botulinum toxin injections can quell them. In some families, as well as the cosmetic problems, severe tongue lacerations from nocturnal tongue biting can be a significant cause of disability (Jarman et al. 1997b). The inheritance is autosomal dominant.

TREATMENT OF TREMOR

Treatment of tremor in childhood generally depends on the underlying cause. Children with the mild, non-specific jerkiness described above, do not need treatment but require reassurance and observation. Holmes tremor is generally a very disabling problem due to destructive lesions involving the red nucleus and neural fibres originated in the cerebellum and substantia nigra. There are multiple causes including ischaemia, haemorrhage, trauma, metabolic disorders, infections, and neoplasms. L-dopa is helpful in some cases of Holmes tremor (Velez et al. 2002; Katschnig-Winter et al. 2015). Levetiracetam may also have a role (Ferlazzo et al. 2008). Surgery has also been used including ablative procedure such as subthalamic lesions in the fields of Forel, Vim thalamotomy, pallidotomy, and more recently DBS of the globus pallidus interna or ventralis intermedius nucleus of thalamus (Peker et al. 2008; Espinoza Martinez et al. 2015). Unfortunately, Holmes tremor in childhood is often the result of severe head trauma with diffuse brain injury, and there are limited options for treatment.
Myoclonus is a complex hyperkinetic movement disorder characterised by sudden, brief, involuntary jerks of a single muscle, or a group of muscles (Zutt et al. 2015). In negative myoclonus, rather than a sudden muscle contraction, there is sudden muscle inhibition with loss of tone, causing the affected limb to drop under the influence of gravity. In 1949, describing this phenomenon in patients with liver failure, Adams and Foley coined the term ‘asterixis’ from the Greek ‘sterein’ (to fasten or to support).

Subcortical myoclonus has its origin between the cortex and the spinal cord. Caviness (2014) cites examples of subcortical myoclonus and the putative source: myoclonus-dystonia syndrome (basal ganglia); opsoclonus-myoclonus syndrome (brainstem-cerebellar circuits); reticular reflex myoclonus (brainstem reticular formation); and propriospinal myoclonus (spinal cord). The electrophysiological characteristics of subcortical myoclonus are a burst duration of more than 100ms, and absence of cortical excitability (Zutt et al. 2015).

Brainstem myoclonus is characterised by abnormal activity starting in the brainstem and spreading in both rostral and caudal directions, producing bilaterally synchronous, generalised EMG bursts. The duration is longer than cortical myoclonus, being between 50 and 150ms. The burst usually first appears in the sternomastoid muscles, and then spreads up and down the neuraxis, giving a typical appearance when the EMG of multiple muscles is recorded. Clinically, there is bilateral synchronous jerking, with adduction of the arms, and flexion of the head and trunk, and at the elbows. Most jerks are induced by stimuli. Particularly potent in producing brainstem myoclonus are taps in the ‘mantle’ area – the nose, lips and head. However, the jerks can also be produced by loud noises and unexpected visual stimuli.

Brainstem myoclonus can be caused by similar insults to those that cause cortical myoclonus such as anoxia. Both cortical and brainstem myoclonus may appear in the same patient. There is overlap between brainstem myoclonus and startle syndromes such as hereditary hyperekplexia.

Spinal myoclonus is rarely seen in childhood. Spinal segmental myoclonus consists of rhythmic and repetitive, bilaterally synchronous, jerking at rates of 30–130 per minute. This is confined to one or two adjacent body segments, and is often caused by a structural lesion. In propriospinal myoclonus, there is orderly recruitment of muscles innervated by many spinal segments producing trunk flexion. It has been suggested that propriospinal myoclonus arises from a spinal generator, recruiting axial muscles up and down the spinal cord via long propriospinal pathways. However, there has been considerable controversy about this condition, and many patients carrying this diagnosis are thought to have a psychogenic disorder (van der Salm et al. 2010, 2014).

The term peripheral myoclonus is used in the setting of anterior horn cell disease and peripheral neuropathies. The bursts are typically of short duration (<50ms) and may be multifocal. The rather confusing term minipolymyoclonus is sometimes used in this setting. (This is discussed in the Tremor section.)

**Clinical Features of Myoclonus**

It is both the speed, and the brevity of the movements, which help to distinguish myoclonus from other movement disorders.
When the jerks are subtle, it may be difficult to separate myoclonus from fasciculations and myokymia (Espay and Chen 2013). Fasciculations are spontaneous contractions of muscle fibres supplied by a single motor unit. With myokymia there are involuntary, subtle, continuous, rippling and quivering movements of muscles. Both fasciculations and myokymia are usually of lower amplitude than myoclonus, and as a rule, unlike myoclonus, they do not alter the position of the body parts in which they occur.

Many causes of myoclonus are discussed in other parts of the book. Myoclonus dystonia is discussed in the Dystonia section; Benign Neonatal Sleep Myoclonus and Benign Myoclonus of Early Infancy in Chapter 16; myoclonic seizures and the progressive myoclonic epilepsies in the chapter dealing with seizure disorders; and opsoclonus-myoclonus syndrome in the Para-infectious Diseases chapter. As in previous sections, here we focus on a small number of clinically important causes of myoclonus.

<table>
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<tr>
<th>Table 19.7</th>
<th>Some causes of tremor</th>
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<td>Enhanced physiological tremor</td>
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<td>Essential tremor</td>
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<td>Endocrine disorders</td>
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<td>Hyperthyroidism, Phaeochromocytoma</td>
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<td>Recurrent hypoglycaemia, e.g. Insulinoma</td>
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<td>Inborn errors of dopamine metabolism</td>
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<td>Cobalamin and other deficiency disorders</td>
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<td>Kleinfelter syndrome; Fragile X-Tremor-Ataxia syndrome in adults</td>
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<td>Drugs and toxins</td>
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<td><em>Adults and older adolescents</em>: alcohol withdrawal, neuroleptics, lithium, tricyclic antidepressants, cocaine and other stimulants</td>
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<tr>
<td><em>Children</em>: salbutamol and other bronchodilators, valproic acid, chronic inhalation of petrol and organic solvents. Midazolam withdrawal syndrome in acutely unwell infants</td>
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<td>Hydrocephalus (may mimic essential tremor: macrocephaly)</td>
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<td>Other structural/developmental problems</td>
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<td>Bobble-headed doll syndrome, spasmus nutans</td>
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<td>Holmes tremor (especially following head injury)</td>
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<td>Wilson disease</td>
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<tr>
<td>Spinal muscular atrophy and neuropathies (‘contraction pseudotremor of chronic denervation’ may be a better term than tremor)</td>
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<td>Glut-1 deficiency (dystonic tremor)</td>
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When the jerks are subtle, it may be difficult to separate myoclonus from fasciculations and myokymia (Espay and Chen 2013). Fasciculations are spontaneous contractions of muscle fibres supplied by a single motor unit. With myokymia there are involuntary, subtle, continuous, rippling and quivering movements of muscles. Both fasciculations and myokymia are usually of lower amplitude than myoclonus, and as a rule, unlike myoclonus, they do not alter the position of the body parts in which they occur.

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**JERKING IN SLEEP AND DROWSINESS**

Jerking movements as the child drifts off to sleep, and during sleep, are common in typically developing children. This is a frequent cause of concern for parents, who may not be reassured when simply told this is nothing to worry about, and the movements are unlikely to be epileptic.

The many types of jerking movements described in sleep can be confusing for those who are not specialists in sleep medicine, because of their number, and because different terms may be used for the same phenomena. The different types of jerks include rapid eye movement (REM)-related EMG activity, hypnic jerks (sleep starts), faciomandibular myoclonus, excessive fragmentary myoclonus, neck myoclonus and high-frequency leg movements (also known as hypnagogic foot tremor, and alternating leg muscle activation). Apart from REM-related EMG activity and hypnic jerks these are not common clinical problems in children, but they make us aware of the complexity of the movements that can occur in sleep.

**REM Sleep Related EMG Activity**

In normal rapid eye movement (REM) sleep there is a profound inhibition of muscle tone, punctuated by bursts of myoclonic limb twitching. Parents are more likely to be reassured if they are informed that careful study has found these twitching movements are common in both humans and animals, and that they may be necessary for normal brain development. The twitches have been found to be a primary activator of neural networks throughout the central nervous system, and are thought to help instruct the brain about the rapidly developing body. (For a review, see Tiriac et al. 2015.)

**Hypnic Jerks (Sleep Starts)**

With hypnic jerks there are usually one or two whole-body jerks which occur as the person is drifting off to sleep. Typically, there is simultaneous involvement of the muscles
of the trunk and extremities. The abdominal muscles are not primarily involved. During EEG recordings, hypnic jerks can be seen when K-complexes appear, and during arousals (Vetrugno and Montagna 2011). Hypnic jerks can be associated with autonomic activation with transient tachycardia, tachypnoea, and sweating. There may be an associated feeling of sudden tipping backwards, which adults have likened to ‘falling downstairs, over a cliff and into a pit’ (Oswald 1959). At least five different motor patterns have been described with hypnic jerks (Calandra-Buonaura et al. 2014). Hypnic jerks seem to have a subcortical origin, but ‘the description of several physiological types of motor patterns for the same phenomenon leaves uncertainty on its features and pathophysiology’ (Calandra-Buonaura et al. 2014).

Hypnic jerks can occur in a brief cluster in normal people, due to a physiological oscillation between sleep and wakefulness during drowsiness, which has been called the ‘cyclic alternating pattern’ (CAP) (Serino and Fusco 2015). In children with neurological impairment there is a reduction in control of the CAP, and more prominent hypnic jerks may occur. Serino and Fusco (2015) have reported a 27-month-old child with epileptic seizures during sleep, characterised by initial short-lasting tonic posturing followed by hypomotor behaviour with autonomic signs. This child also had prominent jerks on going off to sleep which resembled hypnic jerks but were found to be epileptic in origin. Both the more obvious seizures, and the jerking when going off to sleep, stopped when carbamazepine was prescribed. The authors concluded that when what are thought to be hypnic jerks are clinically seen when K-complexes appear, and during arousals (Vetrugno and Montagna 2011). Hypnic jerks can be associated with autonomic activation with transient tachycardia, tachypnoea, and sweating. There may be an associated feeling of sudden tipping backwards, which adults have likened to ‘falling downstairs, over a cliff and into a pit’ (Oswald 1959). At least five different motor patterns have been described with hypnic jerks (Calandra-Buonaura et al. 2014). Hypnic jerks seem to have a subcortical origin, but ‘the description of several physiological types of motor patterns for the same phenomenon leaves uncertainty on its features and pathophysiology’ (Calandra-Buonaura et al. 2014).

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A not uncommon clinical problem is the child who has had an event which might have been a seizure, and the parents then become aware of the child having hypnic jerks. In this setting, rather than blithely dismissing the parental concerns, getting a sleep EEG in the hope of recording the jerks is probably the most sensible way to proceed. Asking the parents to video an episode can also be helpful.

**MYOCLONUS AND ENTEROVIRUS 71 INFECTIONS**

Since it was identified in 1969, enterovirus 71 has caused epidemics in multiple parts of the developed and developing world (Ooi et al. 2010). Mostly it causes a mild illness, but in outbreaks there can be severe neurological sequelae. Typically, there is a prodrome lasting around 3 days, where there may be hand-foot-and-mouth disease or herpangina, with vomiting and fever, followed by neurological manifestations (Huang et al. 1999). (With hand-foot-and-mouth disease, there is a papulovesicular rash on the palms and soles, and multiple oral ulcers. In herpangina there are multiple oral ulcers that mainly affect the posterior pharynx.)

Multiple reports have noted a high incidence of myoclonus in children with enterovirus 71 infections (Ishimaru et al. 1980; Huang et al. 1999; Nguyen et al. 2014). The myoclonus appears to be subcortical on clinical and EEG grounds. Huang et al. (1999) described 41 children with neurological complications of enterovirus 71. They identified three neurological syndromes: (1) aseptic meningitis (three patients), (2) acute flaccid paralysis (four patients), and (3) rhombencephalitis (37 patients). (Three patients with rhombencephalitis went on to develop acute flaccid paralysis.) Myoclonus, which ranged in severity from mild myoclonic jerks during sleep, to very frequent myoclonus during both sleep and waking hours, was present in 32 patients (86%), and was the most common initial symptom. In seven patients there was transient myoclonus followed by the rapid onset of respiratory distress, shock, coma, loss of the doll’s eye reflex and apnoea. Five of these patients died within 12 hours of admission. Three of the patients with acute flaccid paralysis, had myoclonus and tremor before the onset of paralysis.

Myoclonus can be caused by other infectious diseases (see Table 19.8), but it seems to appear more commonly with enterovirus 71 infections. Therefore, in the child who presents with fever and myoclonus, with or without hand-foot-and-mouth disease or herpangina, the possibility of enterovirus 71 infection should be considered, and preparations made in case the child suddenly deteriorates.

**MYOCLONUS AND ANTIBIOTICS**

Many drugs can cause myoclonus (see Table 19.8). The beta-lactam antibiotics penicillin and the cephalosporins, may cause myoclonus as part of a generalised encephalopathy with lethargy, confusion, agitation, and coma (Grill and Maganti 2011). In this setting subtle myoclonus of the eyelids can be a clinical clue that the patient is in non-convulsive status epilepticus. With the cephalosporins, the risk seems higher if there is renal impairment. The possibility that the antibiotic is responsible for myoclonus and other seizures, may not be considered as the patient is often febrile and unwell, and may have structural abnormalities of the brain. Keskin and Konkol (1993) described a 3-year-old boy with hemimegalencephaly, who on three separate occasions when given antibiotics for a febrile illness, had a marked exacerbation of his pre-existing seizure disorder. On two of these occasions he was given oral cefadroxil, and on the other oral amoxicillin. During the exacerbations, the seizures lasted for 40–50 seconds and occurred up to 40 times a day. There was ‘clenching of the teeth and generalised tonus and myoclonus of the extremities, followed by respiratory irregularities’. In response to parental concern about the antibiotics being responsible, the child was given intravenous penicillin when well, and immediately had a tonic seizure.

When an antibiotic is responsible, myoclonus or generalised seizures usually develop within days of it being introduced (Bhattacharyya et al. 2016). The EEG is abnormal, showing epileptiform activity, triphasic waves or slowing. The symptoms settle a few days after the antibiotic has stopped. The mechanism appears to be inhibition of neurotransmission
at GABA<sub>a</sub> receptors, and consequent central excitotoxicity (Bhattacharyya et al. 2016).

Such reactions should be contrasted with Hoigne syndrome which is an acute, toxic, nonallergic reaction described following the intramuscular administration of procaine penicillin (Silber and D’Angelo 1985). The multiple potential manifestations of Hoigne syndrome occur almost immediately following the injection, and include abnormal taste and vision, hallucinations, a sense of impending death (anorg ani) and generalised convulsions. There is then a rapid recovery.

### SEROTONIN SYNDROME
#### (SEROTONIN TOXICITY)

In the serotonin syndrome there is a classic triad of mental state changes, autonomic hyperactivity, and neuromuscular abnormalities (Boyer and Shannon 2005). Myoclonus can be a feature and has been seen in several reports of serotonin syndrome in childhood (Gill et al. 1999; Arora and Kannikeswaran 2010; Grenha et al. 2013). As well as myoclonus, a frequently described sign is clonus and hyper-reflexia which is much
more obvious in the legs than the arms. The clonus occurs spontaneously, and is also easily induced. In the child who is extremely agitated or has marked rigidity, these signs may be difficult to detect. In a severe case, serotonin syndrome is a medical emergency with hypertension, coma, shock, renal failure, rhabdomyolysis and respiratory failure occurring. Treatment is based on the severity of the symptoms, and begins with stopping the offending medication. Benzodiazepines, 5HT antagonist such as cyproheptadine, nitroprusside and ventilation with muscle paralysis may be required (Volpi-Abadie et al. 2013).

With the widespread use of selective serotonin reuptake inhibitors (SSRIs), it is important to consider serotonin syndrome in children with unexplained sudden encephalopathy. Symptoms usually begin within 24 hours of an increased dose of an SSRI, or the addition of another serotonergic agent. Rarely a single but relatively high dose of an SSRI can provoke serotonin syndrome (Gill et al. 1999).

It is important to remember that there are a large number of medications that may unexpectedly have a serotonergic action (Volpi-Abadie et al. 2013). These can be unwittingly given to a child already on an SSRI. The medications include herbal supplements such as St. John’s Wort, over-the-counter cold remedies containing dextromethorphan, amitriptyline, ondansetron and narcotic agents including tramadol and pethidine. Certain combinations such as fluoxetine and carbamazepine, and fluoxetine and risperidone, seem to carry a higher risk of serotonin syndrome (Volpi-Abadie et al. 2013).

**TREATMENT OF MYOCLONUS**

It is important to look for reversible causes of myoclonus such as a metabolic disturbance or a drug effect. Some epileptic causes of myoclonus respond well to sodium valproate and/or benzodiazepines. Epileptic negative myoclonus may be very responsive to ethosuximide (Oguni et al. 1998). Treatment of the progressive myoclonic epilepsies can be very difficult. A full discussion of the treatment of epileptic myoclonus can be found in Chapter 16. Often treatment of cortical forms of myoclonus involves polytherapy with sodium valproate, levetiracetam, piracetam and benzodiazepines used in various combinations. Botulinum toxin can be used for focal and segmental myoclonus. Treatment is based on the underlying cause and more detailed information can be found in the reviews of Kojovic et al. (2011), Caviness (2014) and Zutt et al. (2015).

As with most movement disorders the list of potential causes of myoclonus is huge. Table 19.8 lists some causes.

**EXCESSIVE STARTLE**

Sometimes it can be difficult to separate a startle response from myoclonus. A startle reaction is a normal response to a sudden fright. The stimulus may be a loud sound, or unexpected touch. Neurophysiology has revealed two components to the normal startle response (Brown et al. 1991). The first is a short latency reflex component that starts with an eye blink, and progresses down the body with generalised flexion of the head, trunk and limbs. The second component occurs up to a second later, and is a behavioural response that is influenced by the circumstances of the stimulus.

In a number of conditions, the startle response is enhanced. Hyperekplexia is a neurogenetic condition characterised by hypertonia that is predominantly seen in the trunk or lower limbs, and an excessive startle response easily provoked by touch or noise (Thomas et al. 2013). In severe cases, infants exhibit marked hypertonia from birth that only disappears during sleep. Umbilical and inguinal hernias are frequently present, and are probably the consequence of increased abdominal pressure due to sustained muscle contraction. Noise may precipitate intrauterine startle responses in some cases. The neonatal manifestations of the disease were initially reported as the ‘stiff baby syndrome’ or ‘congenital stiff-man syndrome’ before the condition was fully recognised. There is little or no habituation of the startle reflex. Tactile stimuli, particularly nose tapping are especially effective in provoking the response (Shahar et al. 1991). However, this can induce episodes of prolonged apnoea that require resuscitation, and can be fatal. In this situation flexion of the trunk may immediately relieve the spasm (Vigevano et al. 1989). From 12 months onwards there tends to be a spontaneous decrease in the generalised hypertonia but violent, often repetitive, jerks of the limbs on falling asleep may appear (Andermann and Andermann 1988). In older children unexpected noises can provoke sudden unprotected falls ‘en statue’ with injury. Developmental delay is not uncommon.

Hyperekplexia is caused by mutations in genes responsible for glycine neurotransmission. Two genes encode for subunits of the postsynaptic inhibitory glycine receptor GLRA1 (encoding the α1 subunit) and GLRB (encoding the β subunit) (Thomas et al. 2013). A third, SLC6A5, encodes the presynaptic glycine transporter 2. Further rare mutations have been identified in collybistin (ARHGEF9) and gephyrin (GPHN) which are postsynaptic proteins involved in orchestrating glycineric neurotransmission (Rees et al. 2003). These rare mutations are associated with a more severe phenotype. Hyperekplexia was initially recognised as a dominant condition, but in a recent review of 97 cases, 84% showed recessive inheritance (Thomas et al. 2013). Most patients respond well to clonazepam, which may offer more relief from effects of the startle reactions, than the hypertonia (Tijssen et al. 1997).

An acquired hyperekplexic syndrome can be caused by auto-immune encephalitis, classically associated with glycine receptor antibodies. Other antibodies have also been described. It is more common in adults, but young children can be affected. They have an acquired excessive startle response plus rigidity, and sometimes seizures (Carvajal-González et al. 2014). Investigation other than serum and CSF autoantibody findings can be unremarkable, and it is
syndrome can have unexpected falls with sudden tactile or auditory stimulation. They appear to be awake during the episodes, and in some cases the episodes have similarities to hyperekplexia (Hahn and Hanauer 2012).

Probably the most common type of exaggerated startle reaction in childhood is a psychogenic disorder. With psychogenic startle, on neurophysiology the latency of the response and its EMG signature conform to that of a voluntary movement, rather than a true reflex response (Pal 2011). To a degree the lag between the stimulus and the response can also be identified clinically.

Jumping induced by a startling stimulus has been known for a long time in various populations under exotic names such as 'Jumping Frenchmen of Maine', 'latah' or 'myriachit'. (Tourette, in his famous 1885 paper, discussed these conditions as well as tics.) Saint-Hillaire et al. (1986) based on personal observation of eight cases of 'Jumping Frenchmen' believed the phenomenon was not a neurological disease, but could be explained in psychological terms as operant conditioned behaviour.

<table>
<thead>
<tr>
<th>Deficient enzyme</th>
<th>CSF findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine hydroxylase</td>
<td>Low Homovanillic Acid (HVA)</td>
</tr>
<tr>
<td>GTP cyclohydrolase1</td>
<td>Low HVA, low 5 hydroxyyl indole acetic acid (HIAA)</td>
</tr>
<tr>
<td>Neopterin and biopterin low or normal</td>
<td></td>
</tr>
<tr>
<td>Aromatic acid decarboxylase</td>
<td>Low HVA, low HIAA, high 3-0-methylidopa, high vanillactic acid</td>
</tr>
<tr>
<td>Sepiapterin reductase</td>
<td>Low HVA, low HIAA, normal neopterin, high biopterin and sepiapterin</td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>Increased ratio HVA/HIAA</td>
</tr>
</tbody>
</table>

Table 19.9 Typical CSF findings in inborn errors affecting dopamine metabolism

In adults, parkinsonism is common and is usually caused by idiopathic Parkinson disease (PD). In paediatric practice, parkinsonism is a rare problem with many causes. The core clinical signs of Parkinson disease are bradykinesia, rigidity, tremor and postural instability (Jankovic 2008). All these signs can be seen in children with parkinsonism. A distinction is made between the bradykinesia meaning slowness of movement, and hypokinesia meaning a poverty of spontaneous movements, such as the immobile facial expression seen in adults with Parkinson disease (Berardelli et al. 2001). A typical feature of milder forms of parkinsonism is that with repeated performance of the same task (such as opening and closing the hand while touching the thumb against the fingers), there is a progressive decrement in the amplitude of the movement. As has been emphasised throughout this chapter, patients frequently have multiple movement disorders, and dystonia often coexists with parkinsonism in children.

Parkinsonism in children can be approached on the basis of whether the child presents in infancy or later.
as CP. Treatment of parkinsonism in children can be dramatically effective, and it is important that, although the conditions are rare, children affected by inborn errors causing dopamine deficiency are correctly identified.

Clinical Features

Although there are multiple causes, the clinical features of inborn errors involving dopamine metabolism are similar (Table 19.10). The signs substantially result from dopamine deficiency which in effect is a deficiency of both dopamine and noradrenaline (norepinephrine), as noradrenaline is formed from dopamine. Dopamine deficiency produces hypokinesia, rigidity, tremor, dystonia and oculogyric crises (Grattan-Smith et al. 2002). In addition, noradrenaline deficiency produces ptosis, miosis, profuse oropharyngeal secretions and possibly hypotension. The signs of noradrenaline deficiency may give the false impression that the infant has a neuromuscular disorder. Sometimes there is generalised hypotonia, further complicating the clinical picture. Many of the inborn errors cause both dopamine and serotonin deficiency. The clinical features of serotonin deficiency in infants are not as well established, but probably include disorders of sleep and temperature regulation.

The tremor of dopamine deficiency is typically slow and coarse. It does not usually have the ‘pill-rolling’ character that can be seen in adults with Parkinson disease. Tremor is not seen in all cases, but when present is a most important clue to the diagnosis. Tremor has been described with tyrosine hydroxylase deficiency (de Rijk-Van Andel et al. 2000), 6-pyruvoyl-tetrahydropterin synthetase deficiency (Factor et al. 1991), an undefined disorder of biopterin synthesis (Snyderman et al. 1987), with AADC deficiency (Korenke et al. 1997) and with sepiapterin reductase deficiency (Neville et al. 2005). In a personal case of tyrosine hydroxylase deficiency (de Rijk-Van Andel et al. 2000), 6-pyruvoyl-tetrahydropterin synthetase deficiency (Factor et al. 1991), an undefined disorder of biopterin synthesis (Snyderman et al. 1987), with AADC deficiency (Korenke et al. 1997) and with sepiapterin reductase deficiency (Neville et al. 2005). In a personal case of tyrosine hydroxylase deficiency (Grattan-Smith et al. 2002), arm tremor was the first definite sign and commenced at 2 months of age. Over time the tremor spread, and also involved the tongue, head and legs. It was coarse and presented a dramatic clinical picture (videos accompany the article). Tremor was present when the infant appeared to be at rest, and with attempts at movement. A tremor study from the tibialis anterior showed rhythmic muscle bursts at 4Hz frequency. The tremor responded rapidly to L-dopa therapy. Recent reviews describing 36 patients with tyrosine hydroxylase deficiency (Willemsen et al. 2010), and 78 patients with AADC deficiency (Brun et al. 2010) have not emphasised the presence of tremor, but when present, tremor is a very important sign raising the possibility of dopamine deficiency.

Oculogyric crises are episodes in which the eyes involuntarily deviate upwards, or upward and to one side. Rarely the movements may be horizontal, or downward, or the eyes may converge. Oculogyric crises were first described following the pandemics of encephalitis lethargica that occurred during and after World War I, in patients who developed parkinsonism (‘post-encephalitic parkinsonism’). The oculogyric crises would appear suddenly, recur repeatedly, and last from seconds to hours, often with associated feelings of anxiety or distress (McCowan and Cook 1928). During an episode the eyes could be lowered voluntarily, but at the cost of increased anxiety. The authors care for siblings with tyrosine hydroxylase deficiency due to mutations in the cyclic adenosine monophosphate (AMP) regulatory component of the gene (Verbeek et al. 2007). The older boy presented at 2 years and 9 months with unexplained CP and had very frequent oculogyric crises that did not seem to trouble him. They disappeared soon after treatment with L-dopa was started. His younger sister had less prominent oculogyric crises but has found that as she is approaching adolescence, despite treatment with L-dopa, she still has occasional oculogyric crises which she finds distressing. Oculogyric crises are a particularly common sign in AADC deficiency (Brun et al. 2010) where they may last hours, and sepiapterin reductase deficiency (Neville et al. 2005). They also occur, among other abnormalities of eye movement, in dopamine transporter deficiency (Kurian et al. 2009). Dopa-responsive oculogyric crises have also been reported with ATP1A3 mutations (Termsarasab et al. 2015).

Neurotransmitter Pathways and CSF Analysis

It is likely that ‘gene panels’ will soon be available to identify the underlying cause in infants with parkinsonism, but at present the analysis of CSF neurotransmitter metabolites is the most useful initial test in suggesting the underlying cause.

Abnormalities of CSF pathways can be viewed in terms of defects in the pathways of the pterins, of dopamine and of serotonin (see Fig. 19.2).
The pterin pathway produces tetrahydrobiopterin (BH4) which is required for the conversion of phenylalanine to tyrosine, tyrosine to L-dopa, and tryptophan to 5-OH tryptophan. There are five steps in the pterin pathway where defects can cause a reduction in BH4. The relevant enzymes are (1) GCH1, (2) 6-pyruvoyl tetrahydropterin synthase, (3) sepiapterin reductase (SR), (4) dihydropteridine reductase (DHPR) and (5) pterin-4alpha-carbinolamine dehydratase. The two conditions that are of particular interest to neurologists are GCH1 deficiency and sepiapterin reductase deficiency. The other pterin disorders usually cause elevated phenylalanine levels, and are therefore detected by newborn screening, and tend to be managed by specialists in metabolic disorders.

Neopterin is generated by the action of GCH1. It is also released by macrophages, and is an immunological marker for the activation of the cell-mediated immune system. Elevated neopterin levels are non-specific, as they can be found in infections, and auto-immune and inflammatory diseases of the CNS (Huber et al. 1984; Dale et al. 2009). Biopertein and dihydrobiopterin (BH2) are the oxidative products of BH4.

There are two enzymes in the dopaminergic pathway whose deficiency produces infantile parkinsonism, tyrosine hydroxylase and AADC. With tyrosine hydroxylase there is pure dopamine deficiency, and its breakdown product homovanillic acid (HVA) is low in the CSF. With AADC both dopamine and serotonin are deficient. Therefore, both the breakdown product of serotonin, 5-hydroxy indole acetic acid (HIAA) and HVA are low in the CSF. In both conditions pterins are normal. At the time of writing, no inborn errors restricted to the serotonin pathway have been found to have a significant role in infancy (see also Table 19.9).

‘TRANSPORTOPATHIES’

Defects in monoamine transporter have been recently recognised, and are a further cause of parkinsonism in infancy. In dopamine transporter deficiency (DTD) there is a mutation in the SLC6A3 gene that encodes the presynaptic dopamine transporter (Kurian et al. 2009, 2011). This mediates the active reuptake of dopamine, and regulates the amplitude and duration of dopamine neurotransmission. The first report described infants presenting with irritability, hypotonia and feeding difficulties, as well as a movement disorder that was initially hyperkinetic, and then evolved into a hypokinetic parkinsonism–dystonia picture. Unusual eye signs were a feature, including ocular flutter, saccadic abnormalities and oculogyric crises. As the disease progressed the children were severely affected with the development of dystonic crises, and life threatening episodes of status dystonicus. All patients became parkinsonian over time. Four of the 11 children had died.

In DTD, there is a raised ratio of HVA to HIAA in the CSF, a finding not seen in other neurotransmitter disorders. It appears to be explained by defective reuptake of dopamine into the presynaptic neuron. The result is an accumulation of extraneuronal dopamine, producing high CSF levels of HVA. The CSF HIAA levels remain normal, as the dopamine transporter does not affect the serotonin biosynthetic pathway.

Treatment of the severe forms of DTD is generally ineffective. Recently three brothers have been reported with DTD who presented at around 10 years of age with juvenile parkinsonism, having previously been normal (Ng et al. 2014). In these three boys, the response to L-dopa was not able to be assessed.

In vesicular monoamine transporter disease, there are mutations in SLC18A2 which encodes the dopamine-serotonin vesicular transporter. Rilstone et al. (2013) described eight individuals from a large family who presented with a loss-of-function mutation in this transporter. All children had global developmental delay, and presented with a picture of dopamine and serotonin deficiency. In one patient, CSF neurotransmitters were normal but in the urine, dopamine and norepinephrine levels were low, with HVA and 5-HIAA elevated. L-dopa treatment was given to four children, and within 1 week resulted in ‘major deterioration, with the appearance of intense chorea and worsened dystonia’. The dose used was not recorded in the article. There was a rapid return to baseline function when the medication was stopped. There was a good response to the dopamine agonist pramipexole, in particular in the parkinsonian features.
A second family has been reported by Jacobsen et al. (2016). Two brothers were severely delayed with profound immobility and bradykinesia. They required nasogastric feeding and orthopedic interventions for subluxation of the femoral heads and thoracic-lumbar scoliosis. They communicated with facial expression, vocalisation, a few words and limited use of a modified Makaton sign language. A 1-week trial of L-dopa at a dose of 1–2mg/kg three times a day in the older sibling, at age 3 years, was discontinued due to worsening of dystonia, however improvement in irritability, drooling and verbal communication was noted. At 14 years, he was given paramipexole, building to a dose of 0.5mg three times daily. He did not tolerate higher doses. Improvement in vocalisation and a reduction in the abnormal conjugate eye movements improved his communication and social interaction. There was no improvement in his gross motor skills, and only a subjective small improvement in dystonia and parkinsonism. CSF neurotransmitters were initially normal apart from a slight low HVA and 5-HIAA levels. There was no improvement in his gross motor skills, and only a subjective small improvement in dystonia and parkinsonism. L-dopa per day, combined with dopa-decarboxylase inhibitor (Grattan-Smith et al. 2002). In conditions where there is both dopamine and serotonin deficiency, the L-dopa can be used particularly in the treatment of tyrosine hydroxylase deficiency, sepiapterin reductase deficiency and in the recessive forms of GCH1 deficiency which present in infancy (Furukawa et al. 1998; Nardocci et al. 2003). The major problem with the use of L-dopa in this setting is the development of severe dyskinetic reactions, even with low doses (Grattan-Smith et al. 2002; Pons et al. 2013). The initial dose of L-dopa (combined with a dopa-decarboxylase inhibitor) should be very low and it should be given in divided doses, for example a total of 0.3mg/kg/day given in four divided doses. To achieve this, dispersible forms of L-dopa such as Madopar Rapid can be used. The dose may then need to be slowly increased over many months.

If with an increase in dose, dyskinesia develops, then it is worthwhile returning to the previous dose, waiting a month or more and then making another attempt to increase the dose. The target dose may be in the realm of 10–15mg/kg of L-dopa per day, combined with a dopa-decarboxylase inhibitor (Grattan-Smith et al. 2002). In conditions where there is both dopamine and serotonin deficiency, the L-dopa can be combined with 5-hydroxytryptophan (5HT), a serotonin precursor. The dose of 5HT ranges from 1 to 16mg/kg and is also given in multiple fractions. 5-HT should be given at the same time as the L-dopa/dopas-decarboxylase inhibitor as this will also prevent its peripheral decarboxylation, reducing side effects and allowing more 5-HT to get into the brain (Roubertie et al. 2012).

SECONDARY NEUROTRANSMITTER DISORDERS

There are many conditions where there can be abnormalities of CSF neurotransmitters, which seem to result from injury to, or malfunction of, neurotransmitter pathways, rather than inborn errors of their metabolism. Low CSF HVA with normal CSF 5-HIAA levels have been found in conditions such as Aicardi-Goutières syndrome (AGS), Lesch–Nyhan syndrome and Rett syndrome. (For a detailed list of the many secondary causes of CSF neurotransmitter abnormalities, see Ng et al. 2015.) Low CSF HIAA levels appearing in isolation are also a common, and perhaps non-specific finding. Ng et al. (2015) have also reported 15 children who had the typical profile of tyrosine hydroxylase deficiency in their CSF, but were negative for mutations both in the tyrosine hydroxylase gene and its promoter region. These children presented with neonatal apnoea, axial hypotonia and limb rigidity. Later they developed features of infantile parkinsonism–dystonia with dyskinesia, and some had oculogyric crises. There was a variable response to L-dopa therapy in this group, and relatively high mortality.

Treatment of Parkinsonism in Infancy

The response to treatment of inborn errors of dopamine metabolism varies according to the severity of the deficit, and the enzyme involved. AADC deficiency may be particularly difficult to treat (Brun et al. 2010; Helman et al. 2014.) This is understandable because the mainstay of treatment of other neurotransmitter disorders, L-dopa, cannot be converted to dopamine because of the enzyme deficit. There is also concern over the use of L-dopa in patients with AADC as it may cause further L-dopa accumulation, with consequent depletion of S-adenosylmethionine, the universal methyl donor (Marcos et al. 2014). Many patients with AADC deficiency receive combination therapy including a dopamine agonist, MAO inhibitor, pyridoxal-5′-phosphate and folic acid. This regime is often of limited efficacy, and as a result in a small number of patients, transfer of the human AADC gene into the putamen has been attempted using adeno-associated viral vectors (Hwu et al. 2012).

There have been excellent recent reviews that look at the complexities of treatment of paediatric neurotransmitter disorders (Roubertie et al. 2012; Marecos et al. 2014; Ng et al. 2015). Here we concentrate on broad principles. L-dopa is used particularly in the treatment of tyrosine hydroxylase deficiency, sepiapterin reductase deficiency and in the recessive forms of GCH1 deficiency which present in infancy (Furukawa et al. 1998; Nardocci et al. 2003). The major problem with the use of L-dopa in this setting is the development of severe dyskinetic reactions, even with low doses (Grattan-Smith et al. 2002; Pons et al. 2013). The initial dose of L-dopa (combined with a dopa-decarboxylase inhibitor) should be very low and it should be given in divided doses, for example a total of 0.3mg/kg/day given in four divided doses. To achieve this, dispersible forms of L-dopa such as Madopar Rapid can be used. The dose may then need to be slowly increased over many months.

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PARKINSONISM APPEARING AFTER INFANCY

A list of the large number of potential causes of parkinsonism can be found in Table 19.11. Parkinsonism occurring after infancy is more easily identified than in infants. The history and investigations, in particular the MRI findings, may help
return to normality; (2) near normality; (3) a substantial but incomplete response and so on, supported by carefully performed before and after videos.) Unfortunately in a number of these conditions, although there may be a good initial response to L-dopa, this is then followed by the early onset of disabling dyskinesia, and progressive loss of efficacy.

Neuronal intranuclear inclusion disease (NIID) typically begins in childhood but it can occur in adults. It is often a multisystem disorder, and may not be a single disease. Possible presentations include ataxia, seizures, autonomic dysfunction and parkinsonism. In children presenting before the age of 5 years, a rapidly progressive cerebellar syndrome is common (Sloane et al. 1994). In older children and adults, behavioral change, swallowing difficulties, parkinsonism and multisystem neurodegenerative features are more prominent. NIID may present with a picture of dopa-responsive parkinsonism (Lai et al. 2010). NIID is characterised pathologically by eosinophilic intranuclear inclusions in neurons of the central, peripheral and autonomic nervous systems, associated with varying degrees of neuronal loss (Malandrini et al. 1998). NIID can be diagnosed by rectal biopsy (Goutières et al. 1990). This does not need to be full thickness, but it should be remembered that the intranuclear inclusions may be found in as few as 10% of autonomic ganglion cells, and the biopsy must be of adequate size to include a sufficient number of these cells (Lai et al. 2010). Among those patients presenting with NIID and parkinsonism, a good initial response to L-dopa is soon followed by the development of dyskinesia and progressive loss of efficacy. Clues that bring the diagnosis of NIID to mind in a person with juvenile parkinsonism include gaze-evoked horizontal nystagmus, oculogyric crises, severe dysarthria and blepharospasm.

### Table 19.11 Some causes of parkinsonism

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-hypoxia</td>
<td>often combined with severe generalised dystonia</td>
</tr>
<tr>
<td>Infections and autoimmune disorders</td>
<td>classically encephalitis, Lethargia but also arboviruses (e.g. Japanese B encephalitis), influenza, post-streptococcal infections, anti-NMDAR encephalitis and basal ganglia encephalitis</td>
</tr>
<tr>
<td>Neuroleptic drug exposure</td>
<td></td>
</tr>
<tr>
<td>Inborn errors of dopamine metabolism</td>
<td></td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>Aromatic amino acid decarboxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>Spergularen reductase deficiency</td>
<td></td>
</tr>
<tr>
<td>Recessive forms GCH deficiency</td>
<td></td>
</tr>
<tr>
<td>‘Transportopathies’</td>
<td></td>
</tr>
<tr>
<td>Dopamine transporter deficiency</td>
<td></td>
</tr>
<tr>
<td>Vesicular transporter deficiency</td>
<td></td>
</tr>
<tr>
<td>‘Genetic’ parkinsonism:</td>
<td></td>
</tr>
<tr>
<td>PARK2 (parkin mutation)</td>
<td></td>
</tr>
<tr>
<td>PARK6a: Pink 1 mutation (PTEN induced putative kinase 1)</td>
<td></td>
</tr>
<tr>
<td>PARK7: (DJ1 protein mutation)</td>
<td></td>
</tr>
<tr>
<td>Rapid onset dystonia-parkinsonism:</td>
<td></td>
</tr>
<tr>
<td>(ATP1A3) mutations</td>
<td></td>
</tr>
<tr>
<td>(FBX07) mutations</td>
<td></td>
</tr>
<tr>
<td>Kufor-Rakeb Disease (Park 9)</td>
<td></td>
</tr>
<tr>
<td>Neuronal intranuclear inclusion body disease</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td></td>
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<tr>
<td>Huntington disease</td>
<td></td>
</tr>
<tr>
<td>Niemann–Pick type C</td>
<td></td>
</tr>
<tr>
<td>Juvenile Neuronal Cereoid-Lipofuscinosis</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar Ataxias 2 and 3</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy agents:</td>
<td>e.g. cytosine arabinoside, amphotericin B</td>
</tr>
<tr>
<td>Toxins: ecstasy, methanol, manganese</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus:</td>
<td>responsive to shunting and L-dopa</td>
</tr>
<tr>
<td>Dercum disease:</td>
<td>painful lipomas are a diagnostic clue</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>5–10 Methylene tetrahydrofolate deficiency</td>
<td>rare presentation. More often developmental delay and a picture similar to subacute combined degeneration</td>
</tr>
</tbody>
</table>

### Table 19.12 Causes of Dopa responsive parkinsonism

<table>
<thead>
<tr>
<th>Cause of Dopa responsive parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inborn errors of dopamine metabolism</td>
</tr>
<tr>
<td>Parkin mutations (PARK 2)</td>
</tr>
<tr>
<td>Kufor-Rakeb disease (PARK 9)</td>
</tr>
<tr>
<td>PLAN ((PLA2G6)-related dystonia-parkinsonism)</td>
</tr>
<tr>
<td>BPAN</td>
</tr>
<tr>
<td>(SO)X6 mutations</td>
</tr>
<tr>
<td>Spinocerebellar Ataxias 2 and 3</td>
</tr>
<tr>
<td>Neuronal intranuclear inclusion disease</td>
</tr>
<tr>
<td>(FBX07) mutations (Park 15)</td>
</tr>
<tr>
<td>Neuronal ceroid-lipofuscinosis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Postencephalitic parkinsonism</td>
</tr>
<tr>
<td>Extrapyramidal myelolysis</td>
</tr>
<tr>
<td>Organophosphate poisoning</td>
</tr>
</tbody>
</table>

Based on Paviour et al. (2004). PLAN, \(PLA2G6\)-associated neurodegeneration; BPAN, beta propeller associated neurodegeneration.
PARKINSONISM-PYRAMIDAL SYNDROMES

In 1954 Davison described five patients with parkinsonism and pyramidal signs. The term pallido-pyramidal disease has been used for such patients. Parkinsonism-pyramidal syndrome seems a better term given the overall paucity of pathological examinations. Although some question the concept of parkinsonism-pyramidal syndromes (Horstink et al. 2010), it can be helpful clinically. When there is both parkinsonism and spasticity, conditions that should be considered include spastic paraplegia type 11 (SPG11), Kufor-Rekab syndrome, mitochondrial membrane protein associated neurodegeneration (MPAN), and FBX07 mutations (Table 19.13). Typically, onset is from 10 years of age onwards.

Mutations in the spastic paraplegia gene SPG11, which encodes spatacisin, cause an autosomal recessive disorder characterised by spastic paraplegia with a thin corpus callosum. There may be intellectual disability followed by progressive cognitive decline, peripheral neuropathy, pseudobulbar palsy and parkinsonism (Anheim et al. 2009). The parkinsonism may be responsive to L-dopa (Guidubaldi et al. 2011). FBX07 mutations (Park 15) cause an early-onset, progressive parkinsonism with associated pyramidal tract signs. In the initial report, spasticity was the first sign appearing in childhood, followed by the appearance of parkinsonism 5–20 years later in three of the ten patients (Shojaee et al. 2008). The response to L-dopa was variable, but one of the patients had a rapid response that was sustained for 4 years. In a subsequent paper describing four patients, parkinsonism was present as an initial sign with the age at onset being between 10 and 19 years (Di Fonzo et al. 2009).

<table>
<thead>
<tr>
<th>Table 19.13 Causes of parkinsonism-pyramidal syndromes</th>
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<tbody>
<tr>
<td>SPG11</td>
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<tr>
<td>Kufor-Rekab disease</td>
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<tr>
<td>MPAN</td>
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<td>FBX07 mutations</td>
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There are a large number of neurological diseases that have no effective treatment, and the early recognition of a treatable problem is clearly a priority. Table 19.14 gives a list of some of the potentially treatable movement disorders. As has been our practice throughout this chapter, we will concentrate the discussion on a number of important causes.

Early recognition and treatment is always a goal, but many of these conditions are rare and difficult to diagnose, having diverse and unusual clinical manifestations. With advances in genetic technology, it is likely that there will be many children unexpectedly found to have a potentially treatable condition. The question will then arise as to whether they have been harmed by the delay in diagnosis? The concept that the earlier a treatment is given, the better will be the outcome, is intuitive and a belief that probably goes back to beyond recorded history. In this setting we need to be cautious, and certain that there is hard evidence that earlier treatment does make a difference, as the prospect that the delay has cost the child a chance of a normal life, is profoundly upsetting to both the parents and the treating doctors.

Glucose transporter deficiency syndrome (GTDS) is well-known as a treatable disorder and is discussed in detail below. It seems logical that early treatment with the ketogenic diet, using ketones as an alternative brain energy fuel to glucose, would produce a major difference in outcome. There is no doubt the ketogenic diet is very effective in stopping seizures (Alter et al. 2015), but long-term studies suggest it may not prevent intellectual disability (Alter et al. 2015; Fujii et al. 2016). Alter et al. (2015) reviewed 13 patients with GTD who had been followed for an average of 14 years, and found that earlier introduction of the ketogenic diet was associated with better outcome in motor skills, but not with improved intellectual and adaptive behaviour scores. The study included two children who started the ketogenic diet within the first months of life, yet had intellectual disability. The authors suggested that ketones may not be able to replace glucose metabolism in all its complexity, particularly in vulnerable regions such as the thalamus and cerebellum, with their diverse associated connections and circuits. They postulated that damage in infancy set the scene for the later development of dystonia, as a parallel to delayed onset dystonia after hypoxic injury to the infant. They speculated that the ketogenic diet, to be maximally effective, may need to be initiated in the neonatal period, which would require a newborn screening programme.

Treatable does not mean curable. Doctors who report improvement in their patients with a specific treatment have a duty to do this in a careful, detached, and scientific manner, and include long-term follow-up (van der Knaap and Kevelam 2014).

As evidence of the enduring nature of the belief that early treatment makes a difference, we need go no further than to Machiavelli who, over 500 years ago, at a time when there was almost nothing in the way of effective treatment wrote: ‘for it happens in this as the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected nor treated in the beginning, it becomes easy to detect but difficult to cure’ (Machiavelli, The Prince 1513).
In anti-NMDA receptor encephalitis, antibodies are directed against the NMDAR. More than 90% of affected patients develop at least three of the following groups of symptoms within 1 month of disease onset: psychiatric disturbance, memory problems, seizures, dyskinesias, decreased level of consciousness, autonomic instability and hypoventilation (Armangue et al. 2012; Titulaer et al. 2013). Facial dyskinesia can be a particular feature. There may be semi-periodic movements where the mouth opens and closes as though gulping, and the tongue protrudes (Kleinig et al. 2008). In young children the presentation can be with status epilepticus with the subsequent development of severe dyskinesias (Matoq et al. 2015). In a review of 577 patients, the MRI of the brain was abnormal in only 33% of patients. Abnormalities in the

<table>
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<th>Table 19.14 Potentially treatable conditions causing movement disorders*</th>
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<td>Condition</td>
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<tr>
<td>Paroxysmal Kinesigenic Dyskinesia</td>
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<tr>
<td>Inborn errors of dopamine metabolism</td>
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<td>Autoimmune disorders including Sydenham’s chorea and NMDAR encephalitis</td>
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<td>Wilson’s disease</td>
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<td>Thiamine transporter 2 deficiency</td>
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<td>Manganese transporter deficiency</td>
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<td>Vitamin B12 deficiency</td>
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<td>Episodic Ataxia type 2</td>
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<td>Glucose Transporter Deficiency</td>
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<td>Cerebrospinal fluid folate deficiency</td>
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<td>Biotinidase deficiency</td>
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<tr>
<td>Cerebral creatine deficiency</td>
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<td>Vitamin E deficiency</td>
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<td>Hydrocephalus: arrested hydrocephalus</td>
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<td>Homocystinuria</td>
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<td>Glutaric Aciduria type 1</td>
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<td>Succinic acid semialdehyde deficiency</td>
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<td>Sandifer syndrome</td>
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<td>Pseudohypoparathyroidism</td>
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<tr>
<td>Hashimoto Encephalopathy</td>
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<tr>
<td>Thyrotoxicosis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Cerebro Tendinous Xanthomatosis</td>
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<td>Beta-ketothiolase deficiency</td>
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*In the first column the condition is listed. In the second column, some brief diagnostic clues are given for those conditions not discussed in the text.
NMDAR, N-methyl-D-aspartate receptor.

MOVEMENT DISORDERS ASSOCIATED WITH AUTO-IMMUNE ENCEPHALITIS

In auto-immune encephalitis, antibodies against cell surface neuronal proteins are diagnostic biomarkers. The antibodies target receptors and cell surface proteins involved in synaptic transmission, plasticity or neuronal excitability (Armangue et al. 2012). Although the clinical manifestations can be severe, there may be a very good response to immunotherapy, and therefore it is important to try to recognise the nature of the encephalitis without undue delay. The spectrum of symptoms includes movement disorders, psychotic behaviour, memory loss, seizures and autonomic dysfunction.
CSF (79%) and in EEGs (90%) were more frequent (Titulaer et al. 2013).

Initial treatment of anti-NMDAR encephalitis usually consists of high dose corticosteroids, intravenous immunoglobulin and/or plasma exchange. However, because these treatments fail in 30–40% of the patients, rituximab is increasingly being used in combination with intravenous immunoglobulin and steroids (Dale et al. 2014). Rituximab and cyclophosphamide, alone or combined, are often used in adults. Because of the potential adverse effects of cyclophosphamide in children (including malignancies, infertility and premature gonadal failure), most paediatricians use cyclophosphamide only when the above treatments have failed. In these cases, cyclophosphamide is often effective. Approximately 80% of patients with anti-NMDAR encephalitis have substantial or full recovery with therapy. Early diagnosis and aggressive treatment seems more likely to produce a good outcome in this condition. However, as with other causes of auto-immune encephalitis, the retrospective and uncontrolled way that data has (by necessity) been collected, carries the possibility of bias (Nosadini et al. 2015).

There is a separate subgroup of patients with encephalitis and movement disorders who are negative for anti-NMDAR antibodies, and have symmetrical basal ganglia lesions on MRI, or have serum antibodies to the dopamine-2 receptor. This condition has been called auto-immune basal ganglia encephalitis (BGE) (Dale et al. 2012). These patients also respond to steroids and intravenous immunoglobulin (Fig. 19.5).

Mohammad et al. (2014b) compared the movement disorders found in anti-NMDAR encephalitis and BGE. Patients with Sydenham chorea were used as a comparison group. They found that a mixed movement disorder was common in both anti-NMDAR encephalitis and BGE. However, features that were more typical of anti-NMDAR encephalitis were repetitive orofacial movements, and violent thrashing and kicking movements. These movements were labelled ‘stereotypies’ and ‘motor perseveration’ because of their patterned and repetitive or ‘looping’ pattern. In the BGE group, akinesia and tremor were more common. Dyskinesia was found in both anti-NMDAR encephalitis and BGE, and did not appear to be useful in separating the two conditions. As a very broad rule in separating the two conditions, if the child has a parkinsonian picture and bilateral inflammatory basal ganglia changes on MRI, BGE is the more likely diagnosis. If the patient has a hyperkinetic movement disorder and a normal MRI scan, then anti-NMDAR encephalitis is more likely.

**HASHIMOTO ENCEPHALOPATHY**

Hashimoto encephalopathy is an encephalopathy associated with positive anti-thyroid antibodies, and is generally corticosteroid-responsive. There are a large number of potential presentations including stroke-like symptoms, tremor, myoclonus, transient aphasia, sleep and behaviour abnormalities, hallucinations, seizures and ataxia (Armangue et al. 2012). In a survey from the United Kingdom that identified eight children, one had myoclonus and another tremor (Gayatri and Whitehouse 2005). The difficulty with this disorder is that the prevalence of anti-thyroid antibodies in children has not been well studied, and a response to steroids in an encephalopathic child is non-specific. Armangue et al. (2012) warn that it is not uncommon for patients with auto-immune disorders such as anti-NMDAR encephalitis to be initially misdiagnosed as Hashimoto encephalopathy, because of the presence of raised anti-thyroid antibodies.

**GLUCOSE TRANSPORTER DEFICIENCY SYNDROME**

In glucose transporter deficiency syndrome (GTDS) there is an abnormality of transport of glucose across the blood–brain barrier. It is usually caused by abnormal function of the enzyme GLUT1 which is encoded by the gene SLC2A1. As well as the primary mediator of glucose transport across the blood–brain barrier, GLUT1 also mediates glucose transport into and out of astrocytes, and into erythrocytes. Once an easily understood condition, GTDS has become increasingly complex with the recognition of a wide range of clinical manifestations. This is not surprising as there remains considerable uncertainty over the mechanisms of utilisation of glucose in the brain by neurons and glia. The metabolic pathways are complex with, for example, lactate once seen as a waste product of metabolism, being now regarded as not only an energy source but a signalling molecule (Benarroch 2014). The early reports of GLUT1 deficiency described severely affected children with early-onset epilepsy, marked developmental delay, microcephaly and spasticity (De Vivo et al. 1991). Over time, it has become clear that movement disorders can be a feature of GTD, especially paroxysmal exertional dyskinesia (PED) (Suls et al. 2008). Many subsequent reports have described a combination of multiple forms of epilepsy, and different movement disorders in affected patients. A not uncommon situation is infantile onset epilepsy giving way to childhood-onset movement disorders (Alter et al. 2015).

Pons et al. (2010) found that dystonia and chorea were relatively common in patients with GTDS, as were intermittent ataxia, a spastic-ataxic gait and intention tremor. Dystonic tremor involving the limbs and voice has been reported (Roubegue et al. 2011). Hully et al. (2015) in a comprehensive review of French patients found that movement disorders were observed in all of 24 cases where adequate clinical information was available. Dyskinesia was found in 83% and chorea in 25%. Ataxia was found in 88%. The abnormal movements mostly affected the buccal-facial areas. Abnormal eye movements were found in 75% of patients, and included strabismus, paroxysmal rotatory or disorganised eye movements and abnormal saccades. In a further, retrospective review of 133 patients with GTDS, using family interviews and medical record reviews, abnormalities of eye movement were the second most common initial symptom after seizures (Akman et al. 2016). Manifestations included eye rolling, eye
fluctuating, eyelid drooping, frequent eye blinks, strabismus, opsinclonus and limitation of upgaze.

Hully et al. (2015) found that focal seizures were the most prominent seizure type during the first year of life in GTDS. Subsequently, between 1 and 2 years, atypical absences (38%) and myoclonic seizures (52%) became more frequent. Myoclonic seizures tended to be associated with a worse long-term outcome.

The movement disorders of GTDS may worsen with fasting or infection. The presence of an exertion-induced movement disorder is a very strong clue to the diagnosis. Both DYT18 (PED) and DYT9 (paroxysmal choreoathetosis with episodic ataxia and spasticity) have been found to be due to SCL2A1 mutations (Klein 2014). In paroxysmal exertional dyskinesia (PED), typically after 5–30 minutes of vigorous walking, leg dystonia develops. (Other causes of PED include dopamine deficiency disorders such as GCH1 deficiency [Dale et al. 2010]. See Chapter 16 for a full review.)

Other episodic manifestations of GTDS include paralytic (especially hemiparesis), lethargy, confusion and migraine (Pearson et al. 2013). Haemolytic anaemia can also occur but is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Haemolytic anaemia can also occur but is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013). Prognathism is uncommon (De Giorgis and Vegiotti 2013).

The diagnosis of GTDS rests on paired CSF/serum glucose measurement and/or detection of SCL2A1 mutations. There can be problems with both and unfortunately, the diagnosis is not always straightforward.

Initial reports of GTDS described a low CSF glucose level of below 2.2 mmol/L but higher levels were subsequently reported, especially in milder cases. (Even the units of glucose measurement vary and can cause confusion. In this chapter the values will be expressed in mmol/L. (To convert: 1 mmol/L = 18 mg/dl.) De Vivo’s group suggested that the laboratory hallmark is a CSF glucose which is usually less than 2.2 mmol/L, but sometimes can be as high as 3.2 mmol/L (Pearson et al. 2013). The CSF/blood glucose ratio is also used, but again there are different views about what is abnormal. In most cases the ratio is less than 0.4 but the cut off for normality has variously been set as between 0.45 and 0.6 (Leen et al. 2013a).

One of the difficulties in analysing CSF glucose and the CSF/blood glucose ratios was the lack of standardised data for age-related normal values. In response, Leen et al. (2012) using data obtained from between 4000 and 8000 patients, published standardised age-related data for CSF glucose, CSF/plasma glucose ratio and CSF lactate. They found that in normals, CSF glucose values were relatively lower in the first year of life. Between 6 and 11 months of age, the 10th centile value was 2.2 mmol/L. Between 12 months and 9 years of age it was 2.6 mmol/L, and from 10 to 17 years it was 2.7 mmol/L. It became higher with increasing age.

Leen et al. (2013a) then analysed the CSF data of 157 patients with genetically proven GTDS, derived from 42 articles in the literature. The CSF glucose levels were below their 10th centile for age in all patients, and below the 5th centile for 143 of 147 patients (97%). The CSF to blood glucose ratio was below the 10th centile for 139 of 152 patients (91%), and was below the 25th centile for all patients with GTDS, except for one patient with an isolated paroxysmal exertion-induced dyskinesia. The CSF lactate level was never elevated in patients with GTDS.

The authors concluded that the typical GLUT1 deficiency syndrome profile was a CSF glucose level at or below the 10th centile, in combination with a CSF to blood glucose ratio at or below the 25th centile, and a CSF lactate level at or below the 10th centile. Apart from patients diagnosed with GTDS, this profile was found in only 0.9% of CSF samples present in their database. In addition, during a 2-year period their laboratory had received 104 requests for SLC2A1 mutation analysis on patients with a documented normal CSF glucose, and none had the mutation. The authors concluded that lumbar puncture should be the first step in the diagnostic workup of patients suspected of having GTDS, and that SLC2A1 mutation analysis should only be done when the CSF findings point to the diagnosis.

It is generally recommended that the lumbar puncture should be performed after a 4–6 hour fast with the blood glucose measured first, so that an elevated level caused by the stress of the procedure, does not add further difficulty with the interpretation of the CSF/plasma glucose ratio. Leen et al. (2013a) noted that the equilibration of glucose between plasma and CSF takes approximately 2–4 hours, and in their study with clinically relevant levels of hyperglycemia (i.e. plasma glucose 7.8–25 mmol/L), the CSF glucose was linearly correlated with plasma glucose.

The genetics of SLC2A1 mutations is complex. In the study of Hully et al. (2015), in 58 patients there were 47 different mutations and 33 were novel. Most were point mutations or small one base insertions or deletions, including 29 missense, ten frameshift, four splicing and ten nonsense mutations. Overall, de novo heterozygous mutations in the SLC2A1 gene are the most common genetic finding in GTDS. Dominant inheritance occurs with Brockmann et al. (2001) reporting GTD affecting five members over three generations. Recessive inheritance has also been reported (Klepper et al. 2009). Not all patients who appear to have GTDS have been found to have SLC2A1 mutations (Klepper 2013).

Traditionally, treatment of GTD is with the ketogenic diet, which is a significant undertaking for the child and family, and not without complications. Other methods have been tried. Leen et al. (2013b) reported four patients with GLUT1 deficiency aged between 15 and 30 years who made a remarkable response to the modified Atkins diet. In a short-duration study, triheptanoin, an odd-chain triglyceride, has been shown to markedly decrease the non-epileptic paroxysmal manifestations of GTD (Mochel et al. 2016). It is of interest that, on multiple occasions, both adult patients with GTD and dystonic tremor described by Roubegue et al. (2011), refused treatment with either carbamazepine or the ketogenic diet. As discussed above use of the ketogenic diet may not be able to prevent intellectual disability.
GTDS exemplifies problems that the clinician faces with potentially treatable conditions. It can present with almost any neurological symptom imaginable, including movement disorders, unusual eye movements, seizures and developmental delay. A history of fluctuating symptoms raises the possibility of GTDS, but these symptoms are commonly reported, and GTDS is rare, with an estimated frequency of SLC2A1 mutations in the Danish population of one in 83,000 (Larsen et al. 2015). Diagnosis requires the relatively invasive approach of a lumbar puncture, and/or genetic testing which is not readily available to most clinicians, and may be expensive and not always conclusive. Analysis of glucose uptake into erythrocytes has also been used in highly specialised laboratories (Yang et al. 2011), but this has not come into widespread use.

The clinician is left in a difficult situation as the diagnosis of GTDS can come to mind with a large number of children, yet very few, if any, will have it. Hopefully, in the future, this situation will improve with more readily available and sophisticated genetic testing. For the present, early-onset absence or myoclonic seizures, movement disorders especially PED, and intellectual difficulties are presentations where the diagnosis of GTDS should be suspected. In the retrospective review of Akman et al. (2016) only nine of 133 patients (7%) had first events reported after the age 2 years. This information may be helpful when the presentation is with epilepsy, but may not be as useful when it is with a movement disorder.

**CEREBRAL FOLATE DEFICIENCY**

In cerebral folate deficiency (CFD) low levels of 5-methyltetrahydrofolate (5MTHF) are found in the CSF in the presence of normal folate metabolism outside the nervous system (Ramaekers and Blau 2004). Two forms of CFD have been identified (1) Mutations in the folate receptor 1 (FOLR1) (Steinfeld et al. 2009) and (2) CFD due to autoantibodies to the folate receptor (Ramaekers et al. 2013).

We will discuss CFD due to mutations in FOLR1 gene first. In 2009, Steinfeld et al. reported an inherited brain-specific folate transport defect that was caused by mutations in the folate receptor 1 gene (FOLR1), coding for folate receptor alpha. Three patients carrying FOLR1 mutations developed a progressive movement disorder, psychomotor decline, and epilepsy with onset in the second year of life. All had low MTHF levels in their CSF and they responded to treatment with folic acid (a 5-formyl derivative of tetrahydrofolate). MRI revealed profound hypomyelination. Cario et al. (2009) also described a brother and sister with FOLR1 mutations, with the older brother more seriously affected. Pérez-Dueñas et al. (2010) reported a boy with homozygous FOLR1 mutations adding more detailed clinical information. Progressive ataxia developed in the second year of life, with a broad-based gait, instability and jerky tremor in the upper limbs. At the age of 26 months, he had continuous and generalised choreic movements, and multiple, asynchronous myoclonic jerks which prevented him from standing or walking. Tonic-clonic seizures and cognitive decline were also features. Folinic acid (30mg/day) completely controlled the seizures within a month, and significantly reduced the myoclonic jerks and chorea. Consistent with the timing of the onset of symptoms, MRI showed diffuse abnormalities of the myelination of the white matter of the cerebral hemispheres, but with preservation of the myelin that had been deposited early in life.

Grapp et al. (2012) found mutations in FOLR1 in ten patients who presented in a similar fashion to the previously described cases. There was developmental regression, often with autistic features, seizures and ataxia. MRI revealed profound cerebral hypomyelination and cerebellar atrophy. Inheritance was autosomal recessive. The age at onset was mainly in the first 2 years of life. The seizure disorder was severe with frequent myoclonic, atonic and tonic-clonic seizures, as well as episodes of status epilepticus. Two older patients, aged 13 and 15 years, respectively, had a severe polyneuropathy. One mildly affected patient showed a very good response to folic acid treatment.

Although rare, FOLR1 mutations need to be considered in children with the combination of regression, seizures, ataxia and movement disorders. Particular clues are (1) onset in the second year of life, and (2) extremely low CSF concentrations of 5MTHF; separating this from the more common non-specific reduction seen in multiple different conditions (Pérez-Dueñas et al. 2010; Grapp et al. 2012). For example, in the patient described by Pérez-Dueñas et al., the CSF concentrations of 5MTHF was 2nmol/L with a normal range of 48–127nmol/L.

The other form of CFD is due to autoantibodies. Ramaekers et al. (2013) have described a number of clinical syndromes due to autoantibodies to the folate receptor. In the infantile form, onset is from around the age of 4 months with marked irritability, sleep disturbance, poor developmental progress, deceleration of head growth, ataxia, dyskinesia and spastic paraplegia. Seizures develop in about one-third. The full-blown clinical picture does not manifest until the age of 2.5 years. In undiagnosed cases, visual disturbance begins around the age of 3 years and leads to progressive visual loss, while progressive hearing loss occurs from the age of 6 years. Other presentations include (1) a spastic ataxic syndrome after the age of 1 year without cognitive impairment; (2) infantile autism with and without other neurological deficits; and (3) progressive dystonia or schizophrenia in adolescence or early adulthood.

Elevated levels of folate receptor autoantibodies have been reported in as many as 50–75% of children with autism spectrum disorder (ASD) (Frye et al. 2013; Ramaekers et al. 2013). Frye et al. (2013) found that folate receptor autoantibodies were present in 75% of 93 children with ASD, but only a third of these children improved when given folic acid orally. Complicating the picture is that higher levels of milk intake have been found to be associated with an increased risk of having folate receptor autoantibodies, but without clear abnormalities of folate function (Berrocal-Zaragoza et al. 2009).
A difficulty with the diagnosis of CFD is that there are many causes of low CSF MTHF levels including perinatal asphyxia, infection and conditions such as Rett syndrome (Pérez-Dueñas et al. 2011). Pérez-Dueñas et al. (2011) found that low CSF 5-MTHF levels were relatively common, and most often represented a non-specific manifestation of neurological dysfunction, rather than a disorder of folate transport or metabolism. Mangold et al. (2011) came to the same conclusion believing low CSF 5-MTHF levels frequently represent a final common pathway of different mechanisms that impair CNS metabolism, rather than a specific disorder. Willemsen et al. (2005) have also expressed similar doubts. Therefore, at the time of writing there is uncertainty over the incidence and boundaries of CFD caused by autoantibodies. Nevertheless, it is a potentially treatable condition that needs to be kept in mind.

The recommended treatment of CFD is folic acid in doses at 0.5–3mg/kg/day (Ramaekers et al. 2013), with the doses of 3–5mg/kg/day suggested for mutations in the FOLR1 gene (Steinfeld et al. 2009). Supplementation with folic acid is contraindicated as it may exacerbate the CSF 5MTHF deficiency (Hyland et al. 2010). If a low CSF 5MTHF has been found, even if it is thought to be a non-specific finding, it seems prudent to consider a trial of treatment with folic acid.

BIOTINIDASE DEFICIENCY

Biotin is a cofactor for the human carboxylases, and biotinidase cleaves biotin from biocytin allowing it to be recycled. With biotinidase deficiency there is a variable inability to recycle biotin. There is resultant dysfunction of: (1) pyruvate carboxylase resulting in accumulation of lactic acid and alanine; (2) propionyl-CoA carboxylase, (3) 3-methylcrotonyl-CoA carboxylase, and (4) acetyl-CoA carboxylase which result in the accumulation of multiple organic acids (Wolf 2011). Many countries have newborn screening programmes for the early detection of biotinidase deficiency. It also does not typically cause a movement disorder, but it may cause basal ganglia calcification (Schulz et al. 1988), and radiological abnormalities of the caudate, putamen and basal ganglia (Wolf 2011). It is a condition where early diagnosis and treatment can make a great difference, and therefore it will be discussed here briefly. There are a wide range of clinical manifestations of biotinidase deficiency including respiratory problems (stridor, apnoea and hyperventilation), feeding difficulties, early-onset seizures which are difficult to treat (tonic-clonic, myoclonic or infantile spams), hypotonia, ataxia, cognitive deficits, immunodeficiency, optic atrophy and sensorineural hearing loss (Wolf 2011, 2013). The presence of alopecia, often combined with atopic and seborrheic dermatitis, is a particular clue, but is not always present. Older individuals may present with sudden visual loss, optic neuropathy and spastic paraparesis and may be thought to have multiple sclerosis or neuromyelitis optica (Bottin et al. 2015). The patient described by Bottin et al. (2015) was an athletic young adult who had previously been completely normal.

Metabolic findings in biotinidase deficiency include increased lactate in blood and CSF and increased serum ammonia. There may also be a compensated metabolic acidosi. There are increased quantities of organic acids in the urine, including, in particular, elevated 3-hydroxyisovalerate, which strongly points to the diagnosis (Wolf 2011). However, metabolic abnormalities are not always found, especially in young children. Treatment is with biotin 5–10mg orally per day. Higher doses have been used.

THIAMINE TRANSPORTER-2 DEFICIENCY

Thiamine transporter-2 deficiency (TTD) (previously known as biotin-responsive basal ganglia disease) is a recessive disorder that should be suspected when there are recurrent episodes of subacute encephalopathy, especially when combined with MRI lesions in the caudate and putamen. It was first reported by Ozand et al. (1998) in ten patients of Middle Eastern origin, but it has been found to affect multiple ethnic groups (Debe et al. 2010; Yamada et al. 2010). Typically, onset is around the age of 2–4 years. The episodes may be provoked by a viral illness. Manifestations include confusion, eye movement disorders, dystonia, ataxia, feeding difficulties and seizures. Untreated, the child may die or be left with generalised dystonia and epilepsy. The typical MRI findings include abnormalities of the central part of the head of the caudate, and part or all of the putamen (Ozand et al. 1998; Alfadhel et al. 2013). However, the abnormalities may be widespread, and include abnormal signal change bilaterally in the thalamus, globus pallidus, white matter, brainstem and cortex (Alfadhel et al. 2013; Kevelam et al. 2013).

Over time, other presentations of TTD have been found including onset of intractable seizures in the first year of life, combined with symmetrical bilateral abnormalities of the caudate, putamen and thalamus (Yamada et al. 2010); a Leigh-like syndrome in infants (Kevelam et al. 2013; Ortigoza-Escobar et al. 2014); adults with seizures and a picture of Wernicke’s encephalopathy with bilateral MRI abnormalities in the medial thalamus and periaqueductal region (Kono et al. 2009); and a 15-year-old girl presenting with rapid onset proximal, progressive ophthalmoplegia and fatigue, whose MRI revealed bilateral signal changes in the caudate nuclei and putamen, combined with periaqueductal abnormalities (Fassone et al. 2013). Another child presented at age 4 years with paroxysmal dystonia that went on to become a generalised dystonia (Ortigoza-Escobar et al. 2014).

In the original paper of Ozand et al. (1998), most children responded very well to biotin. However, there was one child who did not make a good response. Another child was given
thiamine as part of a ‘vitamin cocktail’ (the dose was not given in the paper), and did not appear to have a beneficial response. Subsequent studies have established that the condition is caused by mutations in SLC19A3, encoding hTHTR2, one of two enzymes that transport thiamine into the brain (Zeng et al. 2005). Hence the name thiamine transporter-2 deficiency (TTD) is appropriate.

SLC19A3 only transports thiamine, and it is not clear why biotin is beneficial in some children. Lack of biotin reduces the expression of SLC19A3 (Vlasova et al. 2005). Tabarki et al. (2015) have suggested that high dose biotin may increase the activity of the multiple carboxylases for which it is a cofactor, resulting in an overall improvement of the energy production system, which is impaired in thiamine deficiency. It has become clear that biotin alone should not be given to children with TTD. In the study of Alfadhel et al. (2013), six of the 18 patients had recurrent crises when treated with biotin alone, but after the addition of thiamine, the crises stopped (Alfadhel et al. 2013). In a subsequent study of children with TTD, ten were given biotin plus thiamine, and ten were given thiamine alone (Tabarki et al. 2015). The mean age was 6 years in both groups. There was no difference in outcome between the two groups in the number of recurrences, the neurological sequelae, or the brain MRI findings. The only difference was the duration of the acute crisis which lasted 2 days in the first group and 3 days in the second. Given that biotin may have an additive non-specific effect, an approach would be to give both thiamine and biotin at the time of initial presentation, and thiamine alone after a month or so. The dose of thiamine is between 10–40mg/kg/day (Ortigoza-Escobar et al. 2014) with Tabarki et al. using 40mg/kg/day for all 20 children. The dose of biotin that has been used has varied between 1–12mg/kg/day.

Ortigoza-Escobar et al. (2014) have recommended that a trial of thiamine should be given to each child presenting with acute dystonia. Because of the diversity of clinical presentations this should be extended to any child who, on clinical or radiological grounds, has a picture suggestive of Leigh syndrome (Fig. 19.9) or Wernicke encephalopathy. Probably both thiamine and biotin should be used acutely. While awaiting genetic confirmation the finding of extremely low levels of free-thiamine in the CSF may be a useful clue to the diagnosis (Ortigoza-Escobar et al. 2016).

GLUTARIC ACIDURIA TYPE 1 (GLUTARIC ACIDEMIA TYPE 1)

Glutaric aciduria type 1 (GA-1) is an autosomal recessive disorder of amino acid metabolism caused by the deficiency of glutaryl-CoA dehydrogenase activity. The typical biochemical findings are the accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaric acid and glutaryl carnitine in the blood, urine, CSF and brain tissue (Funk et al. 2005; Kölker et al. 2011). Untreated, approximately 90% of patients will sustain severe neurological damage in an acute encephalopathic crisis which is often precipitated by febrile illnesses, immunisation, or surgery (Kölker et al. 2011). In the review by Kölker et al. (2007) of 185 symptomatic patients, most had had crises, and these occurred at a median age of 9 months (range 1–37 months). Ninety-five per cent of the crises occurred by 2 years of age.

Following such crises there is destruction of the caudate and putamen and severe damage to the child, who is left permanently incapacitated with dystonia and other movement disorders, and sometimes spasticity. Intelligence may be preserved. Treatment after a crisis is usually not effective, and the emphasis is on trying to diagnose the condition before these occur. Many countries have newborn screening programmes for this reason.

Macrocephaly is an important clue to the diagnosis of GA-1. It may be present at birth, or there may be rapid head growth in the first few months of life (Kyllerman et al. 1994). In the review by Kölker et al. (2007), of a total of 279 patients found to have GA-1 by various methods, more than 70% had macrocephaly. There may also be non-specific features such as irritability and slight delay in reaching milestones. Benign macrocephaly (known by many names including benign enlargement of the subarachnoid spaces) is common whereas GA-1 is rare. The presence of widening of the anterior temporal and sylvian CSF spaces is typical of GA-1, and has been given many names including temporal hypoplasia, frontotemporal atrophy and a ‘batwing’ appearance (Harting et al. 2009). This appearance is not specific, and can be seen in otherwise normal infants (Amit et al. 1990). However, given the consequences of delayed diagnosis, screening for GA-1 should be performed if there is any doubt.

The combination of macrocephaly, the characteristic widening of the opercula, and basal ganglia lesions, has been regarded as pathognomonic for GA-1 (Kyllerman et al. 1994; Brismar and Ozand 1995). The widening of anterior temporal and sylvian CSF spaces was felt to be evidence of early-onset damage in GA-1, before any crises occurred. However, in patients diagnosed before symptom onset and treated, these findings can regress (Harting et al. 2009). The widening of the extra-cerebral spaces may predispose to the development of subdural haematomas (Osaka et al. 1993), and a misdiagnosis of child abuse.

Apart from the crises, there are other presentations of GA-1. Kyllerman et al. (1994) found that a slowly progressive dyskinetic, dystonic disorder, or a motor incoordination syndrome with attentional problems, developed in 25% of cases. Strauss et al. (2007) identified six children in whom hypotonia of the trunk was recognised between 2 and 3 months of age, independent sitting was delayed, and a movement disorder emerged gradually between 4 and 6 months of age. They were found to have abnormalities of the caudate and/or putamen in what was described as an ‘insidious’ onset.

Onset beyond the first 3 years of life, and in adults, has also been described with GA-1. Fernández-Alvarez et al. (2003) described a 16-year-old girl with GA-1 who presented with a 3-year history of hand tremor with dystonic posturing of the left arm, and some mild developmental
problems. She did not have a large head, but MRI scan revealed bilateral injury to the putamen and diffuse white matter changes more prominent frontally (Fig. 19.10). White matter abnormalities are a common finding in late-onset GA-1, and it is usually the MRI abnormalities that point to the diagnosis. (For a review, see Fraidakis et al. 2015.)

As well as the three most important radiological signs of GA-1 (widening of the operculum, abnormalities of the caudate and putamen and diffuse white matter changes), there may be other abnormalities. These have been summarised by Harting et al. (2009) in a study of 38 patients. Delayed myelination, may be present early on. Harting et al. also found that abnormalities of the globus pallidus were present in half the patients. These occurred in combination with striatal changes following a crisis, or as isolated lesions in patients without crises. Other structures involved were the substantia nigra (16%), dentate nuclei (11%) and thalamus (5%).

Treatment of GA-1 is the domain of metabolic specialists and will only be briefly mentioned. It consists of a low lysine diet with lysine-free, tryptophan-reduced amino acid supplements, carnitine supplementation and emergency treatment of any illness that has the potential to provoke a crisis (Kölker et al. 2007).

CEREBROTENDINOUS XANTHOMATOSIS

Cerebrotendinous xanthomatosis (CTX) is a recessive disorder due to a mutation in the gene CYP27A1 resulting in a deficiency in the enzyme sterol 27-hydroxylase. This plays a key role in the conversion of cholesterol to bile acids (Cali and Russell 1991). Elevated levels of cholesterol are found in the plasma. The development of signs is highly variable, and neurological symptoms may not appear until the second or third decade. The early clinical course may be characterised by mild to moderate developmental delay, and intractable diarrhoea. In the second stage of the disease, there are bilateral cataracts, sometimes associated with optic atrophy, xanthomas and neurological deterioration (Cruysberg et al. 1995). Neurological problems include ataxia, pyramidal signs, dementia, epilepsy and polyneuropathy. There may also be premature atherosclerosis and osteoporosis. Movement disorders such as parkinsonism, oromandibular dystonia and myoclonus are usually seen in adults with CTX (Alcalay et al. 2009; Lagarde et al. 2012; Rubio-Agusti et al. 2012). A slowly progressive spinal syndrome may also be seen in adults (Verrips et al. 1999).

MRI findings can be helpful in suggesting the diagnosis of CTX. The earliest and most frequent MRI abnormality is high signal intensity of the dentate nuclei on T2-weighted images (Barkhof et al. 2000). Other grey matter nuclei, including the globus pallidus, substantia nigra and inferior olive can also be involved. MRI may also demonstrate the Achilles tendon swelling. Treatment is with chenodeoxycholic acid which strongly decreases the levels of toxic intermediary bile acids. Early recognition and treatment reduces the risk of permanent neurological sequelae (Yahalom et al. 2013). Mignarri et al. (2014) have developed a ‘suspicion index’ to aid in the diagnosis of CTX, which gives a weighting to the signs described above.

WILSON DISEASE

Wilson disease is an autosomal recessive condition caused by mutations in the ATP7B gene (Patil et al. 2013). This encodes a copper-transporting P-type ATPase involved in both the incorporation of copper into caeruloplasmin, and biliary copper excretion. ATP7B mutations result in an absent or non-functional ATPase with defective synthesis of caeruloplasmin, and defective biliary copper excretion. Copper accumulates in the liver, the brain, and multiple other tissues producing an extraordinary range of clinical features. More than 500 different mutations have been described in the Wilson gene, with 380 having a confirmed role in the pathogenesis of the disease (European Association for the Study of the Liver [EASL] 2012).

In childhood, Wilson disease usually presents with liver disease. The signs of liver disease are not specific, and it is recommended that ‘any liver disease of unknown origin should be considered as Wilson disease until proved otherwise’ (EASL 2012). Liver disease carries the risk of sudden deterioration and fulminant hepatic failure. Other presentations include haemolysis (Czlonkowska 1972), which may be followed by liver failure (Saito 1987). There are many unusual manifestations of Wilson disease. These are described in the recent EASL review (2012). They include gigantism, renal disease including aminoaciduria, nephrolithiasis, hypercalciuria and nephrocalcinosis, and other problems such as cardiomyopathy, myopathy, chondrocalcinosis and osteoarthritis, hypoparathyroidism, pancreatitis, infertility and repeated miscarriages.

Traditionally the neurological presentation of Wilson disease has been subdivided into four different forms: (1) akinetic-rigid, (2) ‘pseudosclerosis’ dominated by tremor, (3) dystonic, and (4) ataxic. However, such is the variability of symptoms that it has been said that every patient with Wilson disease has their own unique movement disorder. In a review from Brazil of 119 patients with Wilson disease, with a mean age at symptom onset of 19.6 years, the following symptoms were observed: dysarthria (91%), gait disturbance (75%), risus sardonicus (72%), dystonia (69%), rigidity (66%), tremor (60%) and dysphagia (50%) (Machado et al. 2006). Less frequent manifestations were chorea (16%) and athetosis (14%). Seizures (4%) and pyramidal signs (3%) were not commonly seen.

Risus sardonicus results from dystonic involvement of the facial and oral muscles, producing retraction of the upper lip and mouth opening. It is well demonstrated in
the illustrations that go with Wilson’s 1912 paper, and may be accompanied by a generally apathetic facial expression. [Risus is the Latin word for laughter, and sardonicus refers to Sardinia. An explanation of this term favoured by Wilson is that it derived from eating the Sardinian ranunculus. Pausanias, in the second century AD, wrote of Sardinia: ‘The whole island if free of lethal drugs except one weed; the deadly herb looks like celery, but they say if you eat it you die of laughing’ (Giddens 2009). Risus sardonicus is also used to describe the facial expression in tetanus and strychnine poisoning.]

The classic tremor of Wilson disease is a high amplitude proximal tremor, seen when the fingers are held close to the nose, with the shoulders abducted and elbows flexed, giving a ‘wing-beating’ appearance. Other tremors seen in Wilson disease include a rest tremor, intention tremor, and an action tremor when trying to write or drink from a cup (Hoogenraad 1996).

The wide range of potential manifestations of Wilson disease is illustrated by the report of a 9-year-old child of presenting with transient hemiparesis and encephalopathy (Carlson et al. 2004), and a 22-year-old man who developed oxcarbazepine-responsive paroxysmal kinesigenic dyskinesia after treatment started (Micheli et al. 2011).

Wilson disease can also present as a primarily psychiatric problem such as deteriorating school performance, combined with personality and behaviour changes. Zimbrean and copper is a very useful test, and in children baseline copper is usually elevated. Wilson disease patients with the decreased caeruloplasmin in the circulation. Free copper is also used to describe the facial expression in tetanus and strychnine poisoning.]

Whether this has a parallel with white matter changes seen in familial aceruloplasminemia, and in heterozygotes for Wilson disease (EASL 2012; Patil et al. 2013). With acute liver disease, the caeruloplasmin can be in the normal range. If there is no liver disease, the 24-hour urinary copper excretion may be in the normal range in Wilson disease.

Approximately 20% of Wilson disease heterozygotes have decreased levels of serum caeruloplasmin (EASL 2012). This can cause diagnostic difficulties if the child, for example, has a mild non-specific tremor. In this setting, if the MRI scan and 24-hour urinary copper are normal, and there are no Kayser–Fleischer rings, then Wilson disease is unlikely. Urinary copper excretion is higher in heterozygotes than in controls but it rarely exceeds the normal values (EASL 2012).

Kim et al. (2006) reviewed the MRI findings of 50 patients with Wilson disease. The mean age of the patients was 10.2 years, with an age range of 3–16 years, meaning the patients represented a paediatric population. There were three groups based on the initial MRI findings. In Group 1 there were 23 children where the MRI was normal. In Group 2 there were 15 children where the MRI showed increased signal intensity in the globus pallidus on T1-weighted images. T1-weighted abnormalities were also seen in the putamen, midbrain and caudate nucleus. There were no abnormalities on T2-weighted imaging. In Group 3 there were 12 children. Ten (83%) showed increased signal on T2-weighted images of the putamen followed by eight with increased signal in the caudate nucleus (67%), seven in the globus pallidus (58%), six in the thalamus (50%), five in the midbrain (42%) and one in the pons (8%).

There is an impression that the T1-weighted changes are associated with liver disease, and the T2-weighted changes are due to brain injury, but the situation is complex. Kim et al. (2006) found that neurological symptoms were present in four of the 23 patients in Group 1; two of the 15 in Group 2; and 11 of the 12 patients in Group 3. Six patients in Group 3 showed reversion of the high-signal-intensity lesions on T2-weighted images after therapy, suggesting to the authors that the changes were due to focal gliosis or oedema.

Diffuse white matter hyperintensity can also be seen in MRI of patients with Wilson disease (Barbosa et al. 2007). Whether this has a parallel with white matter changes seen following herpes simplex encephalitis discussed above, where damaged neurons are thought to release antigens promoting secondary immunological injury, as far as the authors are aware has not been investigated. In adults with Wilson disease, brainstem changes can give rise to the ‘sign of the giant
panda’ and ‘her cub’ (Liebeskind et al. 2003), but these seem less frequent in children.

Treatment of Wilson disease, and the difficulties of genetic testing (not only are there a large number of mutations, but most patients are compound heterozygotes), are subjects in themselves and beyond the scope of this chapter. The average paediatric neurologist will order serum copper and caeruloplasmin many, many times before encountering a case of Wilson disease. Nevertheless, as a potentially treatable problem with a broad range of neuropsychiatric presentations, it needs to be always considered.

MANGANESE TRANSPORTER DEFICIENCY

Autosomal recessive mutations in the genes SLC30A10 and SLC39A14 cause two distinct forms of manganese transporter deficiency (Tuschl et al. 2012, 2016). In both conditions, whole blood manganese levels are grossly elevated and manganese accumulates in the brain. Children typically present with dystonia between the ages of 2 and 15 years. There may be parkinsonian features with a poor response to L-dopa. Intellect seems to be preserved. MRI of the brain shows a typical appearance on T1-weighted sequences with hyperintensity of the globus pallidus, putamen, caudate, subthalamic and the dentate nucleus with sparing of the thalamus and ventral pons (Tuschl et al. 2012). Other clinical features of SLC30A10 mutations include liver impairment with raised transaminases, unconjugated hyperbilirubinemia, polycythemia and depleted iron stores. In contrast, patients with SLC39A14 mutations do not develop polycythaemia or liver disease, and it appears that manganese does not accumulate in the liver in this disorder. Treatment with disodium calcium edetate infusions can produce clinical and radiological improvement in both conditions (Stamelou et al. 2012b; Tuschl et al. 2016).

RADIOLOGICAL FINDINGS IN BASAL GANGLIA DISEASE

In children with movement disorders, the MRI of the brain can be extremely helpful in making a diagnosis. A person highly skilled in MRI interpretation can be of untold value in this setting. As discussed above, there are a number of conditions where a specific diagnosis is suggested by the MRI scan appearance alone, including PKAN, BPAN, manganese transporter deficiency and cerebrotendinous xanthomatosis. Added to these is Alexander disease where there are abnormalities of the white matter and basal ganglia with contrast enhancement (van der Knaap et al. 2001) and MEGDEL (3-methylglutaconic aciduria with sensori-neural deafness, encephalopathy and Leigh-like syndrome) where there is a distinctive putaminal ‘eye’ in the second stage of the disease (Wortmann et al. 2015).

Even when the MRI findings are not diagnostic, certain patterns of involvement may be helpful in narrowing down the differential diagnosis. Conditions that should be considered based on particular patterns on the MRI scan, can be found in Tables 19.15–19.21 (pp. 1071–1072). Characteristic examples are provided in Figures 19.3–19.13 (pp. 1073–1075).

BASAL GANGLIA CALCIFICATION

There are numerous causes of basal ganglia calcification. Livingston et al. (2013) have outlined a systematic approach including the following adjectives to describe the appearance of the calcification: (1) spots, (2) lines, (3) rock, (4) blush, (5) gyriform/band-like and (6) reticular. The detection of calcification using MRI scan is improved by the use of techniques such as gradient-echo and susceptibility-weighted imaging. Nevertheless, CT remains a more sensitive test (La Piana et al. 2016).

Fahr syndrome is a well-known, but confusing term, probably best replaced by ‘Primary Familial Brain Calcification’. Clinical manifestations are varied, and include psychiatric features, movement disorders, ataxia, headaches and seizures. Onset can be from childhood to the adult years. Three genes have so far been found to cause the syndrome: 1. SLC20A2 (sodium dependent phosphate transporter 2), 2. PDGFB (platelet-derived growth factor beta), and 3. PDGFRB (platelet-derived growth factor receptor beta) (Taglia et al. 2014).

Aicardi-Goutières syndrome is a condition with multiple genetic causes as discussed above. In a review of 110 patients with AGS, calcification was found in the basal ganglia in 77% of patients, in the white matter in 74% and in the dentate nucleus in 15% (La Piana et al. 2016). Severe calcification was associated with TREX1 mutations, and early age at onset. Other common findings in this study were cerebral atrophy (92%) and leukoencephalopathy (99%). Early features include temporal lobe swelling, followed by atrophy with temporal horn dilatation, and global cerebral atrophy (Vanderver et al. 2015).

Table 19.21 lists causes of basal ganglia calcification. A more detailed list can be found in San Antonio and Arzimanoglou (2005).
Table 19.15  Bilateral putaminal +/- caudate lesion +/- thalamic lesions +/- globus pallidus

- Acute severe asphyxia
- Infectious and postinfectious causes, e.g. mycoplasma, measles
- Acute disseminated encephalomyelitis (usually with bilateral asymmetrical white matter lesions)
- Mitochondrial disorders (including MEGDEL with putaminal ‘eye’)
- Wilson disease
- Huntington disease
- Sulphite oxidase/molybdenum co-factor deficiency (severe form plus cavitation of the white matter)
- Radiation & chemotherapeutic agents (plus white matter changes)
- Organic acidurias e.g. propionic aciduria (also involvement of dentate nucleus and cerebellum)
- Glutaric aciduria type 1 (usually after catastrophic deterioration. Widening of anterior temporal and sylvian CSF spaces is an important clue)
- GM1 & GM2 gangliosidosis: thalamus particularly involved
- Haemolytic-uraemic syndrome
- Toxins, e.g. methanol poisoning
- Thiamine transporter deficiency (bilateral lesions in the central part of the head of caudate are a strong clue)
- Autosomal dominant necrotizing encephalopathy (especially thalamus with diffusion restriction)
- Infantile bilateral striatal necrosis (multiple causes including ADARI mutations)
- Vigabatrin effect (T2 hypertensities involving thalami, globus pallidus, dentate nuclei, brainstem and corpus callosum. See Pearl et al. 2009)
- The list is huge. These are just some examples.

Table 19.16  Bilateral caudate nucleus lesions

- Huntington disease (plus atrophy putamen and cerebellum)
- Neuroacanthocytosis
- Lesch–Nyhan disease

Table 19.17  Causes of bilateral globus pallidus lesions

- PKAN (‘eye of the tiger’ sign) and other NBIA syndromes
- Mitochondrial disorders (especially pyruvate dehydrogenase deficiency and Kearns–Sayre syndrome)
- Manganese overload (manganese transporter mutations, liver failure and total parenteral nutrition. Changes are best seen on T1-weighted imaging) (see also Fig. 19.8)
- Carbon monoxide poisoning and other causes of hypoxia
- Kernicterus (Fig. 19.7)
- Canavan disease
- Dentatorubropallidolysian atrophy
- Creatine deficiency (MR spectroscopy is diagnostic, showing absent creatine with normal spectral pattern of other metabolites)
- Sulphite oxidase/molybdenum co-factor deficiency (milder forms may show isolated bilateral globus pallidus involvement)
- L-2 hydroxy glutaric aciduria (GP is usually more involved than caudate and putamen. There is also a leukodystrophy which may be confined to the U fibres. The dentate nucleus of the cerebellum is also involved)
- Bilateral anterior choroidal artery obstruction
- Succinic acid semi-aldehyde dehydrogenase deficiency (there may also be abnormalities of the white matter, subthalamic nucleus and dentate nucleus of the cerebellum)
- Cerebrotendinous xanthomatosis (more prominent than bilateral GP changes is increased signal in dentate nucleus and cerebellar white matter plus cerebellar atrophy)
- Tyrosinaemia (also multiple hepatic nodules)
- Wilson’s disease (mainly with hepatic involvement and best seen on T1-weighted imaging)
- Neurofibromatosis type 1 (presumed hamartomas)
- Late infantile GM1 Gangliosidosis (more commonly bilateral thalamic involvement)
- Glutaric aciduria type 1 (increased signal in globus pallidus bilaterally may be seen without abnormalities of caudate or putamen in asymptomatic patients without encephalopathic crises. In this setting, as well as GP changes, there may be widening of anterior temporal and sylvian CSF spaces, and diffuse white matter abnormalities)
- PKAN, pantothenate kinase–associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; MR, magnetic resonance; GP, globus pallidus.

Table 19.18  Subthalamic nucleus lesions

- Mitochondrial disorders including SURF 1, and complex 1 mutations
- Succinic acid semi-aldehyde dehydrogenase deficiency (occasional finding)
- Kernicterus (in acute phase there can be impressive, symmetrical T1 hyperintense lesions of the STN and globus pallidus)
- Chronic liver failure (T1 increased signal can be seen in STN, globus pallidus and substantia nigra)
- Acute near total asphyxia (bilateral changes in ventrolateral thalamus, posterior putamen, hippocampus and perirolandic cortex are usually more prominent)

Subthalamic nucleus (STN) changes are usually seen in association with other brain abnormalities and are not an isolated finding. See Bosemani et al. (2014) for detailed review.
Table 19.19 Abnormalities of the dentate nucleus of the cerebellum

**Conditions where dentate abnormalities can be prominent**
- Langerhans cell histiocytosis
- Cerebrotendinous xanthomatosis
- Maple syrup urine disease (in neonatal form, swelling of dentate nuclei, brain stem and corticospinal tracts)
- Succinic acid semialdehyde dehydrogenase deficiency (dentate nuclei may be swollen)
- Metronidazole toxicity (plus involvement of splenium of corpus callosum)

**Conditions where dentate abnormalities are usually associated with multiple other brain abnormalities**
- Mitochondrial disorders (see Fig. 19.9)
- Glutaric aciduria type 1 (widening of anterior temporal and sylvian CSF spaces is an important clue)
- L-2 hydroxy glutaric aciduria
- Aicardi-Goutières syndrome
- Peroxisomal disorders
- Krabbe disease
- Merosin-negative muscular dystrophy
- Neurofibromatosis type 1 (presumed hamartomas)
- Alexander disease

Dentate abnormalities can also be seen following multiple intravenous injections of gadolinium based contrast agents (on unenhanced T1 images; globus pallidus can also be involved)
- Glut-1 deficiency (Hully et al. 2015)
- Vigabatrin effect

See McErlean et al. (2010).

CSF, cerebrospinal fluid.

Table 19.20 Delayed myelination

This is common in children with delayed development but if severe, the following should be considered.

- HABC syndrome: hypomyelination and atrophy of basal ganglia and cerebellum (typically delayed myelination and cerebellar atrophy are detected, but absent putamen is overlooked) (Fig. 19.11)
- Pelizaeus-Merzbacher disease
- 18q-syndrome
- Cerebral folate deficiency (*FOLR1* mutations)
- Allan-Herndon-Dudley syndrome

HABC, hypomyelination with atrophy of the basal ganglia and cerebellum.

Table 19.21 Causes of basal ganglia calcification

- Primary familial brain calcification (Fahr syndrome)
- Infections: cytomegalovirus, toxoplasmosis, HIV, tuberculosis, cystercerosis
- Inflammation: lupus erythematosus
- Genetic auto-inflammation (AGS)
- Tumours, including calcified gliomas of the basal ganglia
- Endocrine disorders: hyperparathyroidism; hypoparathyroidism & pseudohypoparathyroidism
- Post-hypoxia
- Toxins: chemotherapy/radiation in treatment of leukaemia
- Mitochondrial disorders including *POLG1* mutations
- Cerebral folate deficiency (mutations in *FOLR1*)
- Biotinidase deficiency
- Carbohydrate deficient glycoprotein syndrome
- Cockayne syndrome
- Dihydropteridine reductase deficiency
- PKAN and associated NBIAs including BPAN
- Krabbe disease
- Carbonic anhydrase 11 deficiency syndrome.
- Neurofibromatosis type 1

PKAN, pantothenate kinase-associated neurodegeneration; NBIAs, neurodegeneration with brain iron accumulation syndromes; BPAN, beta propeller associated neurodegeneration.
Figure 19.3  (a) Axial T2 weighted images show asymmetric increased signal in the globus pallidus and putamen on both sides, with caudate involvement on the left, in a 2-year-old child with a mitochondrial M14487TC mutation. (b) Axial T2 weighted image showing bilateral hypointensity in the substantia nigra and putamen in the same child. (Courtesy Dr Biju Hameed, Bristol, UK.)

Figure 19.4  Axial T2 weighted image of a 3-year-old child with fucosidosis, showing the typical findings of bilateral symmetric hypointensity of the globus pallidus and diffuse hypomyelination in the white matter. (Courtesy Dr Damien Grattan-Smith, Atlanta, USA.)

Figure 19.5  Axial T2 weighted image of a 4-year-old child with basal ganglia encephalitis demonstrating symmetrical increased signal and swelling of the caudate and putamen on both sides. The globus pallidus is spared.

Figure 19.6  (a) Axial T2 weighted image shows bilateral hypointense signal in the substantia nigra in a 15-year-old girl with PLA2G6 associated neurodegeneration. (b) Axial T2 weighted image shows bilateral hypointense signal in the globus pallidus in the same patient. (Courtesy Dr Biju Hameed, Bristol, UK.)
Figure 19.7  Axial T1 weighted image of a neonate with bilirubin encephalopathy (kernicterus), demonstrating increased signal in the globus pallidus bilaterally. (Courtesy Dr Biju Hameed, Bristol, UK.)

Figure 19.8  Coronal T1 weighted image of an 11-year-old boy with congenital porto-systemic shunt and chronic liver disease. There is increased signal intensity in the globus pallidus bilaterally. This is thought to be related to manganese deposition. (Courtesy Dr Damien Grattan-Smith, Atlanta, USA.)

Figure 19.9  In a 20-month-old child with Leigh syndrome: (a) Axial T2 weighted image shows bilateral destructive changes in the putamen. (b) Axial T2 weighted image shows bilateral increased signal in the subthalamic nucleus. (c) Axial T2 weighted image shows increased signal in the dentate nuclei of the cerebellum. (d) Axial Diffusion Weighted Index image also demonstrates increased signal in the dentate nuclei of the cerebellum indicating recent involvement. (Courtesy Dr Biju Hameed, Bristol, UK.)
Figure 19.10 Axial FLAIR image demonstrates bilateral putaminal atrophy in a child where no definite underlying diagnosis was made. (Courtesy Dr Damien Grattan-Smith, Atlanta, USA.)

Figure 19.11 Coronal T2 weighted image of a 12-year-old child with hypomyelination with atrophy of the basal ganglia and cerebellum (HABC) demonstrating cerebellar atrophy and delayed myelination. The characteristic absence of the putamen is often overlooked. (From Manual of Neurological Signs, Morris JGL, Grattan-Smith P, Oxford University Press, 2013.)

Figure 19.12 Axial T2 weighted image of a 4-year-old child who developed chorea following herpes simplex encephalitis (HSE). The destructive changes following HSE are obvious and there is a diffuse increase in signal in the white matter that was not present in the scans performed prior to the development of the chorea. (From Manual of Neurological Signs, Morris JGL, Grattan-Smith P, Oxford University Press, 2013.)

Figure 19.13 Axial FLAIR image of a child with Acute Necrotising Encephalopathy due to an RANBP2 mutation, showing bilateral increased signal in the thalamus and external capsule.
REFERENCES


Tics and Gilles de la Tourette Syndrome

Robert Ouvrier and Russell C Dale
Tics are involuntary, purposeless contractions of functionally related groups of skeletal muscles; involuntary noises; or involuntary utterance of words. Motor tics are brief, rapid, sudden, unexpected, repetitive and stereotyped. Although they can be voluntarily suppressed for variable periods of time, they cannot be resisted indefinitely. They often predominate in facial, head and shoulder muscles. Typical movements include eye blinking, contractions of neck or shoulder muscles, sniffing or snorting. Tics are the most frequent abnormal movements in childhood and may be seen in 20–30% of otherwise healthy children. Several large case series have been reported (Shapiro et al. 1988; Fernandez-Alvarez and Aicardi 2001).

Tics have a premonitory compulsory component, and a sensory ‘urge’ – indeed tics are sensorimotor phenomena rather than motor phenomena alone. Vocal tics are less common but may be of more serious significance than simple motor tics. The most common vocal tics include throat clearing, squeaking, sniffing and other utterances. Behavioural disturbances, especially attention-deficit–hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) are frequently associated. They are often equally as, or more, disturbing than the movements (Jankovic and Fahn 1986).

In the most recent DSM-5 classification (APA 2013), the term ‘transient tic disorder’ (lasting less than 12 months) has been replaced by ‘provisional tic disorder’ since it is not possible to confirm the ‘transience’ of the tics until at least 12 months after commencement of the tics. After 12 months of tics, the label Persistent (Chronic) motor or vocal tic disorder is applied. If at least one vocal tic has been present during a chronic tic disorder, Tourette syndrome is diagnosed.

Tics are probably caused by some disturbance of the motor system, especially the cortico-striato-thalamo-cortical circuits and the dopaminergic system. Other movement disorders may co-exist with tics, including stereotypies. Sometimes it is hard to differentiate complex tics from compulsions – this is particularly challenging with touching tics or ‘evening-up’ tics, which often have a compulsive element.

Tics and Tourette syndrome are common disorders, and when counselling families it is important to make them aware that tics affect one in 20 boys at some stage in their childhood, and that Tourette syndrome affects one in 200 children. Genetic factors in tic disorders have long been recognised but no single mechanism has been established and environmental factors are probably important. It is very likely that tics and Tourette syndrome have multiple disease mechanisms, as is now recognised in autism. It is likely that complex genetic and environmental factors will contribute.

Management of simple tics does not necessarily require attempts at suppressing abnormal movements, as the condition is benign and often mild. Psycho-education is important for the family. It is important for family, friends and teachers to know that the tics are ‘brain symptoms’ – they are not the child’s fault, and the child ‘cannot help it’. Sometimes, ‘tic breaks’ from the classroom can be helpful, for the child to leave the classroom briefly to release some tics that have been building. Parents often describe a burst of tics at the end of the day after school, which is probably due to the child suppressing tics during the day – such suppression can be tiring, and the child may also be emotional and irritable due to the mental energy required. Such suppression should not be encouraged, but is commonly observed. Psychological approaches have become fashionable and are popular with parents as they are non-pharmacological. ‘Tic reversal’ and other psychological approaches have been shown to be effective, but require trained personnel to deliver such therapies, and require the child to be motivated, which is not always true in young children who often are not very aware of their tics (which is good).

If the child is distressed or bullied or is disrupting his classmates, active treatment may be instituted with clonidine. Generally, neuroleptics should be reserved for significantly impaired individuals, given the high rate of side effects, particularly appetite increase, weight gain and consequent metabolic effects. Neuroleptics with dopamine receptor blockade are generally considered to be more effective, such as risperidone and aripiprazole. Haloperidol should only be used if other neuroleptics fail. Many other agents have been tried and were reviewed by Fernandez-Alvarez and Aicardi (2001).

Treatment of associated disorders is as important as that of the tics. Indeed, screening for ADHD, anxiety disorder and OCD is essential, as these disorders are often more impairing, and more treatable than the tics themselves. The best treatment...
of ADHD remains the use of stimulants such as methylphenidate, despite the fact that stimulants can make the tics transiently worse. There are now a number of studies that describe the benefit of stimulants in children with ADHD and Tourette syndrome. It remains a myth that stimulants are contraindicated for the treatment of ADHD in Tourette syndrome (Cohen et al. 2015) and with careful education and introduction, stimulants can be very effective and useful in this situation. Atomoxetine is an alternative ADHD treatment. Anxiety and OCD should be treated initially with psychological approaches such as education on ‘anxiety management strategies’, and cognitive behavioural therapy. If psychological approaches are inadequate, then medical approaches with serotonin reuptake inhibitors (flouxetine, sertraline) should be considered, and in some cases addition of a low dose neuroleptic, such as risperidone.

**Clinical Features**

The criteria for the diagnosis of Tourette syndrome include: (1) both multiple motor tics and one or more vocal tics must have been present at some time during the illness although not necessarily concurrently (coprolalia and echolalia are often lacking in otherwise typical cases); (2) the tics occur many times daily, nearly every day or intermittently throughout a period of more than 1 year without a tic-free period of more than 3 months; (3) they cause significant impairment in everyday life; (4) onset is before 18 years; (5) the disturbance is not the effect of substances (e.g. excitants) or of a general medical condition.

Comorbid manifestations are present in more than half of cases. Some disturbances may result from the personal and social consequences of the condition. OCD is observed with variable severity in about 30% of the patients.

ADHD is also common, as well as a variety of behavioural and psychiatric problems that may be responsible for as much distress as the abnormal movements.

**Differential Diagnosis**

The disorder should be separated from polymyoclonus and chorea, especially Sydenham chorea. In reality, the most common diagnostic challenge is differentiating tics from stereotypies and compulsive behaviours. If there is a very abrupt, infection-associated onset, then paediatric auto-immune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Snider and Swedo 2004) should be considered (see Chapter 12). PANDAS also causes multiple tics and other abnormal movements and psychiatric manifestations especially OCD. Antibodies to basal ganglia neurons have been reported in such cases and are thought to cross-react with streptococcal antibodies (Church et al. 2003; Singer 2004). More recently, it has been recognised that the abrupt onset of OCD or tics is not always streptococcus-associated, and the term ‘paediatric acute neuropsychiatric syndrome’ (PANS) is used instead. The most notable differentiating factor of PANDAS and PANS versus ‘idiopathic’ OCD and Tourette syndrome is the acute abrupt and dramatic onset seen in PANDAS/PANS, and then the potential for complete remission, which is not typically seen in OCD/Tourette syndrome, which more typically ‘waxes and wanes’. This observation has led to therapeutic attempts using antibiotics, corticosteroids, intravenous immunoglobulin and plasma exchange, although these treatments should be restricted to clear cut cases of PANDAS and PANS, and preferably treated by physicians familiar with these rare entities and more typical OCD/Tourette cases.
Treatment of Tourette Syndrome

In many cases of Tourette syndrome, no specific treatment is required. The best approach is to make a correct diagnosis and inform the parents and child that Tourette syndrome is not a psychological problem and that the tics do not indicate an underlying severe psychiatric or neurological disorder but that ADHD, OCD and anxiety disorders can occur and can be treated. It is important to stress that peak severity of the tics tends to occur at around 10–12 years and that improvement or remission may well occur later.

Behavioural and psychological approaches are increasingly popular and have been shown to be effective including tic reversal therapy (Piacentini et al. 2010). Clonidine may also be effective. In severe cases, dopamine receptor antagonists are indicated. Pimozide is often used because at the low doses (1–4mg/day) that are often effective, it has relatively few side effects (Comings 1990). Several Cochrane Reviews indicate that treatment with haloperidol (which should only be used if risperidone fails), risperidone or pimozide is more effective than placebos, although such agents did have significant side effects (The Cochrane Library 2007). Treatment of associated psychiatric disorders is as important as that of the tics.

In resistant cases electrical deep brain stimulation has been effective (Larson 2008; Schrock et al. 2015).

Outcome

In a majority of cases the outcome is relatively favourable as the tics often tend to become less prominent and/or patients learn to live with this problem. Long remissions are not rare.

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Non-Epileptic Paroxysmal Movement Disorders

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The word paroxysm is derived from the Greek paroxysmos to sharpen or irritate, and a paroxysmal neurological disorder is one where there are recurrent events of neurological dysfunction. There are many benign forms of paroxysmal movement disorder which occur in otherwise typically developing children.

The widespread availability of smartphones means that parents are now able to video events, and this can be of immense value in making a diagnosis. Nevertheless, the history remains the most important single aspect of the diagnostic process. The parents (or witnesses to the event) and the child (if old enough) should be systematically taken through what happened. What was the child doing when the event occurred? What was the first sign of something going wrong? How did the event evolve? Was there alteration of consciousness? Is there anything that reliably stops the events? How long did it last? After it was over, what was the child like? How long before he/she was back to normal?

These are just some of the questions that need to be asked. The parents and child may perceive these questions as an interrogation, or wasting time, when the emphasis should be on what investigations need to be done. The importance of the history needs to be explained to them at the beginning of the appointment, so that they can understand its value, and as accurate a history as is possible can be obtained.

In reviewing the various disorders discussed in this chapter, we were struck by how often the initial description was clear, and confined to a well-defined and easily recognised group of children. Subsequent reports often described a much broader clinical phenotype, not uncommonly with a resultant loss of clarity. For this reason, we make frequent reference to the original papers.

**BENIGN NEONATAL SLEEP MYOCLONUS**

In benign neonatal sleep myoclonus (BNSM) non-epileptic myoclonic jerks begin in the neonatal period. This condition was first described by Coulter and Allen in 1982. The jerks are confined to sleep and stop with arousal. They are never seen in the fully awake state, but may appear in the transition from sleep to wakefulness (Kaddurah and Holmes 2009).

The myoclonic jerks take on many forms and can be unilateral or bilateral, synchronous or asynchronous. They may appear as short clusters that shift sides. In some infants, repeated multifocal jerks continue for 30 minutes or more (Kaddurah and Holmes 2009). The jerking can be violent and the infant may be thought to have generalised tonic–clonic seizures, or even status epilepticus (Turani et al. 2004). The fact that the events are confined to sleep is often not appreciated, and the story of an otherwise well newborn infant having multiple daily seizures, unresponsive to antiepileptic drugs, raises the possibility of BNSM. The absence of facial myoclonus has been cited as a clue to the diagnosis, but mild facial and head myoclonus was found in two of 18 infants with BNSM on video-EEG monitoring (Kaddurah and Holmes 2009).

Rocking the infant, repetitive sounds, holding the limbs and antiepileptic drug therapy have been noted in various reports to make the myoclonus worse (Coulter and Allen 1982; Daoust-Roy and Seshia 1992; Alfonso et al. 1995; Maurer et al. 2010).

In BNSM, the EEG is normal in both the awake and sleep states. The origin of the myoclonus is uncertain. In the study of Daoust-Roy and Seshia (1992), polygraphic recordings showed electromyography (EMG) bursts of greater than 100ms making a cortical form of myoclonus unlikely. Fokke et al. (2011) used sophisticated neurophysiological techniques to study a single infant, and felt the myoclonus arose from a generator in the cervical cord. The myoclonic jerks can appear during all stages of sleep, but are least common during rapid eye movement sleep (Resnick et al. 1986; Daoust-Roy and Seshia 1992).

A positive family history of BNSM has been noted in multiple reports including one family where there were five affected siblings (Vaccario et al. 2003). Afawi et al. (2012) looked at three families with apparently dominant inheritance, and did not find linkage with the KCNQ2 and KCNQ3 potassium channel genes that are mutated in benign familial neonatal seizures.

No treatment is necessary for BNSM. If antiepileptic drugs have been used, these should be stopped. In a review of the
Shuddering attacks were described in great detail by Vanasse et al. (1976) who suggested the events represented ‘an expression of the mechanism of essential tremor in the immature brain’. Although a well-known entity, a PubMed search in December 2016 revealed only six articles specific to shuddering attacks in the literature in English. In a study of 666 children with paroxysmal non-epileptic events referred for video-EEG monitoring, 7% had shuddering attacks (Bye et al. 2000). In a more recent review of paroxysmal non-epileptic events recorded by video-EEG monitoring in 31 children, four of 38 recorded episodes were shuddering attacks (Chen et al. 2015).

With shuddering attacks, the episodes usually last less than 5 seconds (Holmes and Russman 1986). They seem to be a combination of body stiffening and trembling. Typically the head, shoulders and arms are involved, and the movements are symmetrical. The neck may be flexed forwards and the arms abducted, but the exact posture varies. There may be facial grimacing. Parents may describe the episodes as if water was poured down the child’s back, or the child was shivering with cold. The episodes can be very frequent, up to 100 times per day. They may settle down for several weeks only to reappear. There are a large number of listed provoking factors including excitement, fear, anger, frustration and embarrassment (Vanasse et al. 1976). The episodes can also occur spontaneously. During the episodes the child does not have alteration of consciousness, and ictal and interictal EEGs are normal. An EMG recording of an episode showed a similar frequency to essential tremor (Kanazawa 2000).

Onset of shuddering attacks is often in the first year of life, but may not be until 2–3 years of age (Vanasse et al. 1976; Kanazawa 2000). Even later onset has been reported, with patient 3 in the Holmes and Russman study being 6 years old when the events started. The events do not uncommonly continue into childhood. In 12 successive children followed by Jan (2010), complete cessation of the episodes was noted by between 3 and 7 years (mean 5.6 years) of age. Patient 3 in the Vanasse et al. (1976) study was still having events at 9 years of age.

In the study of Vanasse et al. (1976), all six children had a tremor and, in four, it was ‘rather marked’. Essential tremor was found in a parent in five of the children. These findings have not been replicated in subsequent studies, and the current view is that shuddering attacks are not a manifestation of essential tremor. Vanasse et al. (1976) also observed that three of the children had tics, and tics were probably also present in two others. Noting the clinical overlap between shuddering attacks and benign myoclonus of early infancy, Kanazawa (2000) suggested both should be subsumed under the term ‘shuddering attacks in infancy’.

There is also an overlap between shuddering attacks and stereotypes. Patient 3 of Vanasse et al. (1976), at 9 years of age ‘became aware and ashamed of these episodes and tried to restrain herself, hide under the table or go out of the room’. As will be discussed below, rather than having multiple different names for the benign movement disorders of childhood, it seems simpler to use the umbrella term ‘benign polymorphous movement disorder of infancy’ which accurately conveys the diversity of potential presentations.

Shuddering attacks do not respond to antiepileptic drugs. Patient 6 of Vanasse et al. (1976) had a reduction in episodes after being given stimulant medication for hyperactivity. Propanolol was reported to help another child (Barron and Younkin 1992). It seems likely that these are non-specific effects that may have related to a change in the child’s morale, or other non-specific factors, rather than a direct effect of the particular medication. As with many of the benign movement disorders of young children, shuddering attacks may be associated with learning and other difficulties. These should be addressed, but the shuddering attacks themselves simply require explanation.

Benign myoclonus of early infancy (BMEI) was first described by Fejerman and Lombroso in the 1970s (Fejerman 1976; Lombroso and Fejerman 1977), and by Fejerman and others in multiple subsequent reports culminating in a review of 102 cases (Caraballo et al. 2009). Although the term myoclonus was originally used, many different types of movement have been described with this condition. Pachatz et al. (1999) performed video-EEG and polygraphic studies on five infants. The events varied in intensity from single subtle jerks, to obvious spasms. Typically, there were tonic spasms of the limbs with associated shuddering like movements of the trunk. EMG of the tonic limb spasms revealed durations as long as 2 seconds. The EEG was normal during the spasms.

In the large review by Caraballo et al. (2009), age at onset ranged from 1 to 12 months, with a median age of 6.2 months. Multiple different events were recognised including myoclonus, spasms and brief tonic contractions, shuddering, atonia and negative myoclonus, and combinations of these movements. An important diagnostic feature, (recognised from the earliest descriptions of BMEI), was that in 87 infants (85.2%), the events only occurred while the infant was awake. In 15 (14.8%), the events occurred while the infant was...
awake, but also in sleep and drowsiness. Multiple events per day were common, and in 45 (44.1%) of the 102 infants, the movements appeared in clusters. The events stopped between 6 and 30 months of age.

With BMEI, episodes may be provoked by excitement or frustration. There is no developmental delay or regression, and the neurological examination is normal, as are ictal and interictal EEGs. The children are normal at long-term follow-up. Because of the wide variety of movements that can be seen in this condition, and Dr Fejerman’s 40-year involvement in its evolution, Dalla Bernadina (2009) has suggested the term ‘Fejerman syndrome’ be used rather than BMEI.

**UNUSUAL BENIGN MOVEMENT DISORDERS OF INFANCY**

Capovilla (2011) described 23 infants with a benign syndrome of infancy where there are *shaking body attacks*, which were felt to be distinct from the movements of BMEI. The characteristic feature was side-to-side shaking movements similar to the moves of a popular dance of some decades ago (‘the shake’). The movements varied in intensity and could be accompanied by the infant crying. Capovilla et al. (2013) have also described benign ‘head atonic attacks’ in infants, which appear to have an overlap with the features of BMEI.

**Tonic reflex seizures of early infancy** is another unusual benign paroxysmal disorder of the young child (Vigevano and Specchio 2010). Onset was typically in the second or third month. There were tonic contractions, predominantly of the limbs, provoked by shaking, tactile stimulation or sudden postural changes. Upright rhythmic movements were particularly likely to provoke attacks; for example, descending stairs while holding the child in a vertical position. The attacks consisted of sudden, sustained, diffuse tonic contraction, with extension and abduction of all four limbs accompanied by apnoea and cyanosis. There was no impairment of consciousness during the attacks, which usually lasted between 3 and 10s, and were followed by a brief cry. Repeating the provoking stimulus could induce another episode. The physical examination was normal as were ictal and interictal EEGs. The events settled by 4–5 months of age, and the authors felt they may be a manifestation of labyrinthine sensitivity.

Cataltepe and Barron (1993) reported a 3-month-old infant who, when rapidly moved from the vertical to the supine position, developed sudden head and eye deviation to the left, with rapid eye blinking, flexion of the upper extremities and crying. When the head was moved to the midline, the episode stopped. There was no alteration of consciousness. After two or three repetitions the episodes no longer occurred. The episodes stopped in the following 6 months. The authors classified this as a form of *benign paroxysmal torticollis* (see Benign Paroxysmal Torticollis section).

**BENIGN POLYMORPHOUS MOVEMENT DISORDER OF INFANCY**

The great difficulty in dealing with the benign paroxysmal movement disorders of infancy is that there is an extremely broad repertoire of possible movements and considerable overlap between the various recognised entities. Parents told that their child has a particular condition, may be confused when they read about it, and find that their child seems to have atypical features. Rather than trying to force a child into a particular diagnostic group, that in reality is not a good match for the symptoms, it seems sensible to use an overarching term that acknowledges the wide variety of unusual movements that can occur in young children. Fernández-Alvarez (2015) has suggested the use of the terms ‘polymorphic, benign, non-epileptic, paroxysmal, infantile movements’ in this setting. The umbrella term ‘benign polymorphous movement disorder of infancy’ (BPMDI) is useful, as it conveys the variety of manifestations in a way that is easily understood.

Fernández-Alvarez (2015) lists the main characteristics of BPMDI:

1. Paroxysmal events, sometimes in clusters, separated by 3–4 minutes;
2. Short duration;
3. No alteration of consciousness;
4. May appear daily and multiple times per day;
5. Usually triggered by excitement, frustration or postural changes;
6. Normal development and normal neurological examination;
7. Normal ictal and interictal EEG;
8. Onset in the first year of life, mainly between 4 and 7 months; and
9. Self-limited.

Obviously not every feature will be found in every child.

Another characteristic of benign movement disorders as a group, is that they can usually be stopped, at least momentarily, by calling the child or making an unexpected intervention. Sometimes calling the child is enough, but a strong tickle associated with a loud noise may be needed. If the event usually lasts say 3–4 seconds, or comes in a cluster, and is consistently and abruptly stopped by such interventions, then this is good supportive evidence of its benign nature.

**BENIGN PAROXYSMAL TORTICOLLIS**

The name torticollis comes from the Latin words *tortus* (twisted) and *collum* (neck). With torticollis, the head is usually tilted to one side and rotated with the chin pointing to the other side. Torticollis is a common manifestation of cervical dystonia in adults.

Benign paroxysmal torticollis of infancy (BPTI) was first recognised in 1969 by Snyder, who described 12 affected
children. Snyder noted that the onset was most often between 2 and 8 months of age. There were recurrent attacks of torticollis, which could last from 10 minutes to 14 days, but most often the episodes lasted 2–3 days. The head turn was to either side. Snyder found that there could be two to three attacks per month, and the children were normal between episodes. Seven of the 12 children were unwell with vomiting, pallor and agitation at the onset of the attacks. However, the other five appeared ‘perfectly content unless the mother attempts to straighten the head, whereupon the baby cries and opposes the attempt’. At follow-up, the episodes had stopped spontaneously in eight of the children, mostly at around 2–3 years of age. In one child where the episodes were of 10 minutes duration, the episodes stopped at 10 months. In another, whose episodes could last 30 minutes to 7 days, the events did not cease until she was 5 years old. Older children would complain that the ‘house was turning’ during an episode, and in four children the mother noted ataxia during the event.

Snyder performed caloric testing on all 12 children (in half, after the episode had stopped). Ice water applied to the ear canal failed to induce nystagmus in all but three children. Snyder concluded the underlying cause was labyrinthine dysfunction.

Subsequent reports added other features. As well as torticollis, lateral curvature of the trunk and retrocollis could occur in the episodes (Chutkanier 1974). Affected siblings were reported (Lipson and Robertson 1978). The episodes could occur with a striking regularity, with the parents able to predict the day of the next episode (Sanner and Bergström 1979). Hanukoglu et al. (1984) noted a female predominance and that most occurrences commenced early in the morning. However, Drigo et al. (2000) in a larger cohort of 22 children, found that there were ten females and 12 males, and the symptoms occurred on awakening in only half of the children. Drigo et al. also noted that in only 27.3% of cases was the head always turned to the same side, and half of the children also had tortipelvis. Further, they described two children whose episodes were very similar to those described by Cataltepe and Drigo (2000) in the Unusual Benign Movement Disorders of Infancy section. The events lasted only minutes and were characterised by a sudden onset with an abrupt turning of the head and eyes to one side, rapid blinking, flexing of the upper limbs and tears. One of the authors (EF-A) has seen onset of BPTI in the neonatal period.

This diversity of presentations led Drigo et al. (2000) to suggest that BPTI could be subdivided into two forms: (1) a more common, ‘periodic’ torticollis that lasts several hours or days; and (2) a rarer short-lived and ‘paroxysmal’ form, lasting only minutes, and accompanied by ocular signs that are usually not seen in the ‘periodic’ form.

Rosman et al. (2009) described ten personal cases of BPTI and reviewed 103 cases from the literature. Five of the ten children in their series had gross motor delay, and three had fine motor problems. These tended to improve with the resolution of the episodes of BPTI, but three children were left with ongoing motor problems. In their literature review, they found that there was no effective symptomatic treatment of the incidences. They also found that in contrast to Snyder’s original paper, in most subsequent reports caloric and audiometric testing were normal. Yaghini et al. (2016) have described four children with BPTI who responded well to topiramate.

When performed on children with BPTI, EEG and neuro-imaging studies have been normal. Kimura and Nezu (1998) performed surface EMG recordings during an episode of torticollis, and concluded it was a dystonic phenomenon. The view of many authors is that that BPTI is an early manifestation of migraine, or a part of the periodic syndromes of childhood.

Children who may have BPTI need to be carefully assessed. The differential diagnosis is wide and includes seizures, vertigo, gastroesophageal reflux, Sandifer syndrome, dystonic reaction to drugs, ocular abnormalities such as fourth cranial nerve palsies, and posterior fossa and craniocervical junction abnormalities such as atlanto-axial instability, Arnold-Chiari malformation and posterior fossa tumours (Tomczak and Rosman 2012).

Drigo et al. (2000) noted that with BPTI features such as its episodic nature, the trigger factors, the familial association with migraine and the lack of anatomical lesions, raised the possibility of a channelopathy as an underlying cause. Subsequently a father and son with BPTI who had mutations in the PRRT2 gene were reported (Giffin et al. 2002). Cuenca-León et al. (2008) reported another patient with CACNA1A mutation who presented with BPTI as a neonate, and when older, developed benign paroxysmal vertigo of childhood, and subsequently hemiplegic migraine. Roubertie et al. (2008) reported a two-generation family with CACNA1A mutations where various affected family members presented in different ways including with benign paroxysmal tonic upgaze, benign paroxysmal torticollis, and episodic ataxia. Vila-Pueyo et al. (2014) reported two further cases of BPTI with loss of function mutations in the CACNA1A gene, and suggested it may be an age-specific manifestation of defective neuronal calcium channel activity. Dale et al. (2012) have reported a child with a PRRT2 mutation who initially had BPTI, and then developed infantile seizures.

Given the wide variety of reported manifestations, with some children ill during the occurrences where others are untroubled, with episodes that can last minutes or days, and the reports of both CACNA1A and PRRT2 mutations causing similar features, it appears that BPTI is a clinical syndrome of multiple different aetiologies.

**Benign Paroxysmal Vertigo**

The term benign paroxysmal vertigo of childhood (BPVC) was coined by Basser in 1964. He described 17 children (ten girls and seven boys), who had sudden episodes of vertigo. The
onset of the episodes was in the first four years of life, except in two children aged 7 and 8 years, respectively. The attacks were brief, lasting usually less than a minute, and rarely more than a few minutes. The child was well before and after the event and there was no alteration of consciousness during the event. The onset was sudden and ‘in a severe attack the child remains perfectly still, unable to move, stand or even sit without support’. In a less severe episode the child typically ‘clutches the mother or her clothing until the attack ceases’. Pallor was frequently seen, and in some children there was also nystagmus during an attack. Older children described intense vertigo during the episodes. For example: ‘Everything around me is spinning’; or ‘The house is falling over’. The interval between episodes varied, typically being 4–6 weeks, but it could be as short as days or as long as 6 months to a year. The attacks ceased spontaneously, usually after several years, but sometimes after only months.

Basser felt that BPVC might be a form of vestibular neuritis, but it was later suggested that it may be an early manifestation of migraine (Fenichel 1967). Subsequent studies have not clarified the underlying cause. Lindskog et al. (1999) reviewed 19 patients with BPVC. The age at onset was between 5 months and 8 years, and the symptoms disappeared within 3 months to 8 years. At follow-up the patients were aged between 18 and 24 years. One woman initially had BPTI then developed BPVC, and as an adult had migraine. However, overall, only 21% of the group developed migraine. None had persistent vertigo, or a balance disorder. Lindskog et al. concluded that BPVC has a favourable outcome, but is not a precursor of migraine.

Drigo et al. (2001) described 19 patients. Six patients had previously presented with episodes of BPT. Three patients went on to develop migraine, and five developed a ‘periodic syndrome’ with recurrent abdominal pain and cyclic vomiting, leading the authors to also suggest that BPVC is related to migraine. Krams et al. (2010) felt that BPVC might have a worse long-term prognosis than previously reported, but included in their group patients who had episodes of vertigo lasting as long as 7 days, which is not typical of the syndrome described by Basser. Batuecas-Caletrío et al. (2013) followed 27 patients for at least 15 years, and found that 33% went on to develop migraine. Most recently Marcelli et al. (2015) found that ten of 15 children with BPVC developed migraine, and or recurrent vestibular symptoms. The other five patients had never had a headache in their life. In this study, abnormalities on neuro-otological examination were found in three patients during the interictal period, and in four of six children evaluated ‘during migraine attacks, vestibular or dizziness spells, even without clinically evident balance issues’. Both peripheral and central vestibular abnormalities were found.

Although there is a relative paucity of reports of BPVC in the literature, the personal experience of the authors is that it is not an uncommon problem. In an otherwise normal child who has the typical clinical features described by Basser, there are few conditions that realistically come into the differential diagnosis, and investigations may not be necessary.

**TRANSIENT IDIOPATHIC DYSTONIA IN INFANCY**

Transient idiopathic dystonia in infancy (TIDI) was first reported by Willemse in 1986. There has been a subsequent paucity of reports. At the time of writing, the most recent reference found in a PubMed search was by Calado et al. in 2011. The term ‘transient dystonia’ has also been applied to low birthweight infants, who show increased muscle tone in the first year of life that subsequently resolves (Drillien 1970; Sommerfelt et al. 1996). It is obviously important not to confuse the two conditions.

The onset of TIDI is usually in the first 6 months of life. There is dystonic posturing of an upper limb and sometimes the trunk or a leg. The typical arm posture is forearm pronation with hyperflexion of the wrist. When prone with the head elevated from the bed, the affected arm may be rotated, and rests on the dorsum of the hand. If the infant is prone and lying flat on the bed, the arm may be extended backwards. When sitting, the arm may hang down with the fist closed, and the arm internally rotated. The dystonic posturing is often unilateral. It may be bilateral, although often with one side more affected (Deonna et al. 1991). Typically, the dystonic posture disappears with intentional movement; for example, when the infant reaches out to grasp an object. This is the key diagnostic feature separating TIDI from other dystonias. A fine tremor involving the tongue, or trunk and extremities has been noted in some cases (Willemse 1986; Calado et al. 2011). Angelini et al. (1988) described infants who had more abrupt paroxysmal episodes of dystonic posturing.

Two of Willemse’s patients were siblings, and, in the study of Calado et al. (2011), father and child were affected. Motor and intellectual development is usually normal in TIDI. Deonna et al. (1991) reported a slight delay in two of eight infants.

The posturing usually stops before the age of 2 years. Some cases seem to have more prominent dystonia and a more prolonged clinical course; for example, patient 4 of Willemse had Achilles tendon surgery at 2 years of age.

Decreased perfusion of the basal ganglia and left temporo-mesial cortex on single-photon emission computed tomography (SPECT) and decreased glucose metabolism in the basal ganglia and cerebellum on positron emission tomography (PET) have been reported in one patient (John et al. 2000). Worsening of the dystonic posturing apparently induced by cisapride, a 5-HT receptor antagonist, has been described (Angelini et al. 1996). Beltran and Coker (1995) have suggested the possibility of fetal cocaine exposure having a role.

Whether TIDI is a transient form of dystonia, or simply transient posturing that resembles dystonia is unclear, and
as with so many of the transient disorders of infancy, it is likely that reported cases are a heterogeneous group.

How far to pursue investigations in an infant who appears to have TIDI is a difficult question. In a child who otherwise seems normal, and in whom the dystonic posturing completely disappears with movement, no investigations may be necessary. Screening for metabolic disorders, in particular glutaric aciduria type 1, and for GLUT-1 deficiency can be considered. An MRI of the brain will require sedation or anaesthesia, and the yield is likely to be low. As always, discussion with the family is important in coming to a decision as to how far to proceed.

**INFANT MASTURBATION (SELF-STIMULATION OR GRATIFICATION EPISODES)**

The first difficulty with this condition is the word used to describe it. 'Masturbation' is straightforward but carries the stigma of centuries of disapproval. (For example, Stedman’s Medical Dictionary [1961] has the following entry: 'masturbate [L. masturbar]. To excite the genital organs by unnatural means; to practice self-abuse'.)

Nechay et al. (2004) found: 'Parents prefer the term gratification [or even benign idiopathic infantile dyskinesia] to infantile masturbation as there is less social stigma attached to these terms'. However, ‘to gratify’ means ‘to give pleasure’, and not everyone will be happy with this. ‘Paroxysmal hyperkinetic motor syndrome of infancy’ has been suggested by Phillips and Seshia (2013), ‘to avoid cognitive biases such as confirmation, diagnosis momentum etc.’ Both ‘benign idiopathic infantile dyskinesia’ and ‘paroxysmal hyperkinetic motor syndrome of infancy’ lack specificity and would require explanation whenever they were used, given the multiple hyperkinetic dyskinesias of infancy. In addition, the process of replacing a term that is regarded as carrying a stigma, with another word that seems less offensive, carries with it the implication that there is something wrong (or to be ashamed about) with the activity. We feel ‘self-stimulation episodes’ (SSE) is an acceptable term as it is not as blunt as masturbation, but at the same time should not cause confusion.

Although discussed in Still’s paediatric textbook first published more than 100 years ago (Still 1909), SSE continue to be a diagnostic problem for those unaware of the characteristic clinical features. (It is usually only in girls that there is a diagnostic difficulty.) SSE can be mistaken for epileptic seizures (Livingston et al. 1975), abdominal pain (Fleisher and Morrison 1990) and paroxysmal movement disorders (Mink and Nell 1995; Yang et al. 2005). Typically, when an infant is supine, the legs are tightly opposed and the feet crossed at the ankles. There may also be mechanical pressure over the supra-pubic or pubic area. Pelvic thrusting may be prominent. If in a high chair or a child car seat, the infant may press against the restraints. Irregular breathing, facial flushing, sweating, irritable cries, and grunting may give an impression that the child is in pain. The episodes can last minutes to several hours. A fixed and glazed look raises the possibility of altered consciousness, but the episode can be usually stopped immediately by picking up the child. This may produce annoyance, and resumption of the activity as soon as the child is put down again.

Still, and many others since, postulated that the behaviour begins after an episode of local vulval irritation, which sensitises the child to pleasurable sensations arising from genital stimulation. Some young girls have as many as 40–50 episodes per day (Rödöö and Hellberg 2013).

There are a small number of follow-up studies of children with SSE. Bakwin (1973) described three girls. One continued to perform the movements at 4 years of age. Another stopped at 6–7 months, and there had been no recurrence up to the age of 8 years. The third child at 12 months carried a large rag doll with her constantly. She repeatedly threw the doll to the floor, and would rhythmically press her body against it. By 4 years, she rarely exhibited the behaviour, and when last seen she was a medical student. In a more recent study, 12 of 19 girls followed up for an average of 8 years, had stopped the episodes after a mean duration of 66 months (Rödöö and Hellberg 2013).

In a child with the typical clinical features of SSE, no investigations are necessary. It is important to explain to the parents that it is a normal behaviour, more pronounced in some children, and with no worrying long-term consequences. Distracting the child towards more interesting activities may help. Many parents are relieved that their child does not have a serious underlying condition, and may regard the activity with a sense of humour. However, even in this apparently enlightened age, some parents feel upset and ashamed, and may need additional counselling (Franić and Franić 2011). It should be emphasised that SSE cause no harm to anyone, and are natural in a young child. Coercive measures to stop the activity are likely to be bad for both the child and the parents.

**STEREOTYPIES**

The word stereotypy was used in the medical literature as long ago as 1907, when it appeared in Meige and Feindel’s textbook *Tics and their Treatment* (Edwards et al. 2012). However, from the beginning there has been a struggle to provide a clear and easily understood definition of what the word means. Stereotypos have been studied in great detail in animals (Ridley and Baker 1982). When left alone in a cage, monkeys will develop repetitive behaviours, known as cage stereotypies, which usually include pacing backwards and forwards, circling, backwards somersaults and jumping on all fours. Deprivation stereotypos occur when a young animal is separated from its mother at an early age. Rather than pacing backwards and forwards, these animals develop body-rocking, head rolling, self-clasping and self-injurious behaviours such as head banging, self-biting and eye-poking. Once deprivation stereotypos develop, they are very difficult to disrupt. It is felt that cage stereotypos are the response of a normal nervous
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system to an abnormal environment. Deprivation stereotypies, on the other hand, reflect an abnormal nervous system, the result of the early separation and isolation.

Repetitive and rhythmic behaviours are part of normal human development (developmental stereotypies). A study of 20 normal infants during their first year of life revealed a great quantity, and variety, of rhythmic and highly stereotyped behaviours (Thelen 1979). These were most prominent between 24 and 42 weeks of age. At that time, some infants spent as much as 40% of the time they were observed, engaged in such behaviours. Thelen observed 47 distinct movements in the 20 infants. Between 2 and 4 years of age, compulsive-like behaviours are also common in typically developing children (Evans et al. 1997). It is when a single behaviour begins to dominate, and persists, that it comes to attention.

Stereotypies such as hand-flapping have long been recognised as a feature of children with autism and intellectual disability. They are common in Rett syndrome, where a characteristic feature is that children under the age of 10 years, while performing hand stereotypies, tend not to look at their hands (Temudo et al. 2007). In a parallel to the animal data, there is also a high incidence of stereotypies in children placed in institutions at an early age (Bos et al. 2010).

Stereotypies occurring in children without major neurological or behavioural problems received little attention until the paper of Tan et al. (1997). Ten children were described, seven of them being boys. A large variety of movements were seen, the most common being arm flapping and leg shaking. In some children, there was hand posturing that seemed ‘almost dystonic or choreoathetoid’. Facial grimacing was also seen. The movements appeared in multiple different situations including when the child was excited, stressed, concentrating, bored or unoccupied. (With the now widespread availability of smartphones a common scenario is a video of the child performing a stereotypy while strapped into a child car seat.) Tan et al. found that stereotypies usually first appeared early in life with a median age at onset of 12 months. Eight of the patients had additional problems such as mild intellectual disability, speech problems and attention-deficit–hyperactivity disorder (ADHD). Follow-up was available to a maximum age of 11 years in nine children, and the stereotypies had completely stopped in only two. Not uncommonly, the child, when older, restricted the movements to the privacy of his own room.

Subsequently, Mahone et al. (2004) using the term complex motor stereotypies (CMS) described 40 children confirming the clinical features described by Tan et al. (1997). As well as CMS, 25% of their group had comorbid ADHD, and 20% had a learning disability. A family history of stereotypies was identified in 25%, tics in 33%, ADHD in 10%, and mood-anxiety disorder in 38%. Only two children had complete resolution of their stereotypies after a duration of 11 and 12 years, respectively.

Oakley et al. (2015) followed 49 children (31 boys and 18 girls) with stereotypies who, when reviewed, were aged between 9 and 20 years. The duration of follow-up was between 6.8–20.3 years. Only one had stopped performing the stereotypies. However, in most the duration and frequency of the episodes was diminished compared with when they were younger. Further, ‘all denied any current functional impairment related specifically to their movements’. There was a family history of CMS in 39%. Most patients (92%) in the series had at least one comorbid disorder, including elevated levels of anxiety (73%), ADHD (63%), obsessive compulsive disorder (35%) and tics or Tourette syndrome (22%). Neuropsychological testing performed on 57 children with CMS, revealed that on IQ tests, although they were consistently in the average range, they did not perform as well as a comparison group (Mahone et al. 2014). One-third of the CMS group also showed signs of developmental motor co-ordination disorder.

Sometimes during stereotypies, the child can engage in intense imaginative play (Robinson et al. 2014). Reported themes included computer games, cartoons and/or films, fantasy scenes, circus tricks or jokes, and film scenes that included family members. The child may be so immersed in the imaginative play, that they may appear to be in a trance, and the possibility of focal dyscognitive seizures arises. Calling them may have no effect, but a sudden unexpected tickle will usually bring an immediate response and stop the event, making a seizure unlikely.

Movement-related cortical potentials (MRCPs) were studied in ten patients with CMS (Houdayer et al. 2014). MRCPs were not present before the stereotypy indicating that these have a different nature than voluntary self-paced movements. This was not interpreted as indicating that stereotypies are involuntary, as MRCPs can be also absent with tics, and present in patients with conversion disorder where the movements are thought to be involuntary (Houdayer et al. 2014). Magnetic resonance spectroscopy using a 7T magnet compared 18 children with primary CMS, and 24 typically developing controls (Harris et al. 2016). Compared with the controls, children with CMS had lower levels of GABA in the anterior cingulate cortex and striatum suggesting possible GABAergic dysfunction within corticostratial pathways. Interpretation of the results of such sophisticated methods of investigation will need to take account of the statement that many children with CMS make – they like doing the movements.

Stereotypies can be classified as transient or persistent. When persistent they are subdivided into: (1) primary when development is essentially normal, and (2) secondary when they are seen in children with autism, intellectual disability or sensory deficits.

Edwards et al. (2012) argue that with stereotypy ‘the meaning of the term has become so blunted by shifts in meaning that it no longer has sufficient precision to be a useful clinical categorical tool’. There is no doubt that it is difficult to avoid cumbersome definitions of stereotypies. Tan et al. (1997) suggested: ‘involuntary coordinated, patterned, repetitive, rhythmic, non-reflex, non-goal directed motor activity that is carried out in exactly the same way during each repetition’. Wolf and Singer (2008) use the following: ‘repetitive, rhythmic movements that have a predictable pattern and location, seem purposeful but serve no obvious function, tend to be prolonged,
and stop with distraction’. Edwards et al. (2012) felt that the following should be preferred: ‘a non-goal-directed movement pattern that is repeated continuously for a period of time in the same form and on multiple occasions, and which is typically distractible’. Although Edwards et al. claim that such a definition would exclude tics, it would seem to apply very well, for example, to an isolated blinking tic.

It is likely that no simple definition will be found to describe CMS in childhood. The main differentials are complex tics and compulsions. It is not possible to separate these three conditions on the characteristics of the movement alone. Additional difficulties arise because the boundaries are also not always absolutely clear. Both tics and stereotypies can occur in the same patient, and there is often a compulsive element to tics. However, some broad rules usually allow a confident diagnosis to be made. The typical picture of a stereotypy is (1) the movements start early in life, usually in the first 2 years; (2) the same movement persists over time but with some elaboration; (3) although there may be facial grimacing, this is usually in association with arm movements, rather than occurring in isolation; and (4) the child will often say they like doing the movement.

In contrast to tics (1) the movements typically start later, often at around 4–5 years of age; (2) commonly the initial tics are simple in form, such as blinking or facial grimaces, and it is only after several years that more complex movements appear; (3) with tics the movements change over time; for example, blinking may be the first tic, this then subsides, and shoulder shrugging appears, which is then followed by episodes of opening the mouth widely etc.; and (4) the child says they have to do the tic, or they do it because the body part feels stiff, or sore, or itchy.

These criteria will separate tics from CMS most of the time, but there will always be problems; for example, in some children the first tic to appear is a complex movement, and occasionally tics appear in young children. The diagnosis of a compulsion relies on the child saying that the movement is done to ward off harmful events, which they may be reluctant to reveal. However, compulsions are less common than either tics or stereotypies, and usually appear in children well beyond the age of 1–2 years.

Many children with tics say they do not have a premonitory sensation or a need to perform the movement, but when present these features strongly point to the diagnosis of a tic. Enjoying the movement is a very useful pointer to it being a stereotypy: (A father of a child with stereotypies remembered doing them himself as a child, and explained that, when he felt excited, to suddenly add in an arm flap gave him such a thrill that it was ‘almost like taking a drug’.) Distractibility is not a particularly useful differentiating sign, as it is found in both CMS and tics.

The general view on stereotypies has been that there is no effective treatment. However, Specht et al. (2016) used an instructional DVD to assess parent guided therapy. The aim was to make the child more aware of when the stereotypies were occurring. The child was requested to perform the stereotypy for 30 seconds, followed by 60 seconds of rest. This was done five times in succession, twice a day, ideally in front of a full-length mirror. Specht et al. found a reduction in various scores of stereotypies of 15–24%. This assessment was done by the parents, who also administered the treatment. In addition, there was a steep drop out rate. Of the initial 81 participants, 54 provided data at 1 month, 38 at 2 months, and 29 at 3 months.

One approach to stereotypies is to argue that they are a harmless activity that the child enjoys, and treatment is not necessary. In the study of Specht et al. (2016), parental concern seemed to be the driving force behind treatment: ‘Parents express considerable concern regarding disruptions and stigmatization’. In a previous study the same group had noted: ‘These movements are readily suppressed by sensory stimuli or distraction and are of little concern to the patient, whose daily activities are rarely affected’ (Mahone et al. 2004). Hedderly (2016) has observed that after stopping the stereotypies ‘children can express relief, reporting a sense of freedom from the compulsion to perform them’. However, it is unlikely that treatments that only reduce the number of stereotypies will bring such benefits.

The decision as to whether behaviour-based therapies should be used for CMS, will, in the end, hinge on the attitudes of the parent and the treating doctor, with hopefully the child having a say. Parents often worry that the child will be teased, which occurred in 23% of patients in the Mahone et al. study of 2004. However, once other children start asking about CMS, often the child restricts the movements to times when they are alone. If the child is being teased and cannot control the movements among other children, it is a setting where behavioural techniques may be more effective. If the parents perceive the movements as a physical manifestation of joy in their child, they usually are less concerned about them. Some parents find the attention the CMS bring to the child in public upsetting, even if the child is oblivious to it. In this situation it can be explained to the older child that people do not understand their movements, and it would be best to keep them quiet until they get home. One of the potential disadvantages of behavioural therapies to ‘control’ CMS, is that the message for the child is that the movements are ‘bad’, and need to be stopped, even if they enjoy them. If the behavioural therapy fails to control the movements, then the child may be worse off than before, feeling guilt that the movements continue.

The presence of CMS should be seen as a marker for potential problems with learning and attention, which will have a much greater impact on the child’s life than CMS (Oakley et al. 2015).

**PAROXYSMAL TONIC UPGAZE**

In 1988 Ouvrier and Billson described four children with an unusual syndrome they called ‘benign paroxysmal tonic upgaze
of childhood’. The typical features included (1) onset in early life; (2) periods of constant or variably sustained tonic conjugate upward deviation of the eyes; (3) downbeating saccades in attempted downgaze; (4) normal horizontal eye movements; and (5) frequent relief by sleep. The children typically adopted a chin down posture at the times of the upward eye deviation. They were otherwise normal apart from mild ataxia, persistent in one child, and in another appearing at times of illness. There was no deterioration during follow-up which was as long as 15 years. Over time, the abnormal eye movements improved, although two children continued to have minor problems. Investigations including neuroimaging, EEGs and metabolic studies were normal. One patient who died accidentally, had a normal brain post-mortem. In another patient, the mother reported improvement with L-dopa therapy, but this was never independently verified (Ouvrier and Billson 2005).

Ouvrier and Billson concluded: ‘An otherwise normal neurologic and ophthalmic examination coupled with normal neuroimaging of the brain in children with this striking eye movement disorder is sufficient to justify the prediction of a favorable outcome’. At further follow-up, two of the patients were found to have cognitive difficulties (Ouvrier and Billson 2005).

Subsequent reports indicated that structural abnormalities of the brain could be found in children with episodes of paroxysmal upgaze. These included bilateral periventricular leukomalacia (Sugie et al. 1995), hydrocephalus associated with a vein of Galen malformation (Hayman et al. 1998), a pinealoma (Spalice et al. 2000) and demyelination (Senbil et al. 2009). Ataxia was also noted in multiple different reports (Campistol et al. 1993; Guerrini et al. 1998; Lispi and Vigevano 2001). In a study of 16 children only three had normal development and neurological findings (Hayman et al. 1998). This study included patients with rhizomelic short stature and microcephaly. More recently, episodes of tonic upward eye deviation in children have been associated with chromosomal abnormalities (Joseph et al. 2005), Beckwith–Wiedemann syndrome (Skalicky and Billson 2008), CACNA1A mutations (Roubertie et al. 2008; Blumkin et al. 2015) and GRID2 mutations (Hills et al. 2013). Sporadic cases and recessive and dominant inheritance have all been reported.

This is obviously potentially a very confusing situation. Salmina et al. (2012) have made the entirely sensible suggestion that the term ‘benign and transient form of paroxysmal tonic upgaze of childhood’ or ‘Ouvrier-Billson syndrome’, be used for children with episodes of tonic upgaze who are neurodevelopmentally normal, without seizures and with normal neuroradiography. Using these criteria they reported eight personal cases and reviewed 38 from the literature. Even in this carefully defined group (when the information was available), there was considerable variation in the duration of the episodes of tonic upgaze, not only between patients but in the same patient. The events were subdivided into (1) brief paroxysmal events lasting between 3 seconds and 10 minutes which were seen in 50% of cases; (2) intermediate events between 5 seconds and 30 minutes; and (3) long events lasting between 10 seconds and 2 hours. Events lasting more than 24 hours were noted in two cases.

Salmina et al. (2012) in their own series found that the frequency of observed episodes of upward deviation was between two and ten events per day. There was a paucity of information from the 38 cases in the literature, but when reported, a similar frequency was noted except for the paper of Lispi and Vigevano (2001), where the episodes occurred on average every three months. Overall, the onset of most episodes was between 2 weeks and 90 months. In 80% of affected children the age at onset was 24 months or less. Ataxia was present during episodes in 15 of the 46 cases. Five children had persistent co-ordination problems, and borderline motor delay. In seven children, the episodes occurred when the children were unwell with a febrile illness, or following immunisation. In 26 children the episodes stopped between 1 and 48 months. The clinical features of the events were as described in the initial report, with Salmina et al. adding the useful phrase ‘eyes up, chin down’ which captures the characteristic posture.

The term ‘paroxysmal tonic upgaze (PTU) plus’ has been suggested for children who have structural and other abnormalities associated with episodes of tonic upgaze (Zafeiriou 2015). Even if neuroimaging is initially normal, other clinical features help to separate patients with ‘PTU plus’ from Ouvrier-Billson syndrome. For example, of the three children described by Blumkin et al. (2015) with CACNA1A mutations, two had significant motor delay. The other child had ataxia, pyramidal signs, and after the age of 2 years, episodic coma associated with seizures and autonomic symptoms.

Seizures come into the differential diagnosis, but are usually easily separated from PTU. Oculogyric crises need to be considered, as the episodes of upgaze are not clinically distinguishable from brief episodes of PTU. Oculogyric crises occur in treatable conditions such as tyrosine hydroxylase deficiency, where severe neurological abnormalities may be completely reversed with L-dopa therapy, and it is therefore of the greatest importance that they be recognised. (For a full discussion, see Chapter 19.)

No treatment of PTU has been shown to be consistently effective. L-dopa appears to have helped some children (Campistol et al. 1993). Antiepileptic drugs have been tried but without clear success. No clear explanation has been found for the eye movement disorder, but one possibility is abnormal cerebellar dysfunction, particularly of the flocculus (Hills et al. 2013).

**PAROXYSMAL TONIC DOWNGAZE OF INFANCY**

Downward deviation of the eyes in infants may be a sign of serious underlying pathology such as hydrocephalus or kernicterus, but it may also appear in otherwise typically developing children.
Of 19 infants with the ‘setting sun’ sign described by Cernerud (1975), eight had increased intracranial pressure requiring surgical intervention, two had transient signs of increased intracranial pressure which resolved spontaneously, and nine infants showed no signs of illness at all. The sign was elicited by abruptly changing the infant from a vertical to a supine position, or suddenly removing a light source (the ‘eye-popping’ reflex of Perez). Hoyt et al. (1980) examined 242 healthy neonates and found that five had tonic downward deviation of the eyes while awake. This settled after 6 months, and the infants were otherwise normal.

Yokochi (1991) described 13 children with spastic quadriplegia or diplegia, intellectual disability and commonly cortical visual impairment, who had paroxysmal episodes of downward deviation of the eyes lasting several seconds. In five infants these episodes stopped by the age of 2 years. Subsequently brief episodes of tonic downward deviation were described as a benign transient phenomenon in five infants born between 22 and 28 weeks’ gestation (Kleiman et al. 1994). Wolsey and Warner (2006) described two infants who had episodes of downward eye deviation beginning at the age of 5 months, lasting seconds to minutes. During the episodes, one infant had stiffening of the arms and legs, and the other had grasping, flailing upper extremity movements, and retroflexion of the head. The infants were otherwise normal and the events stopped after 6–12 weeks. There was no alteration of consciousness, and investigations such as EEG and MRI of the brain, were normal.

Simonsz et al. (2009) presented a series of infant boys who presented with tonic downgaze, and a chin-up head posture at the age of 3–5 months. They were normal neurologically, and had normal imaging findings. By 2–3 years the inability to maintain upgaze had disappeared. The underlying cause was congenital stationary night blindness.

Although paroxysmal tonic downgaze can be a benign and transient phenomenon, investigations are required including neuroimaging, and careful ophthalmological examination and follow-up. In considering this diagnosis it is important to be aware of the ‘eye-popping’ reflex described by Perez (1972) and discussed by Cernerud (1975) and Wolsey and Warner (2006). In this reflex, there are brief (3–10 seconds) episodes of downward deviation of the eyes associated with lid retraction, appearing after a light source is removed, or following a sudden change of illumination from light to dark. Perez found this reflex to peak between 14 and 18 weeks of age, where it was present in 80% of 308 infants studied.

**SANDIFER SYNDROME**

In 1964, Kinsbourne described five children with contortions of the neck associated with a hiatus hernia. The name Sandifer syndrome has subsequently been used for this condition on the suggestion of Sutcliffe, as a number of the described patients had been under Sandifer’s care, and ‘this was already a specific clinical entity and first appreciated by the late Dr Paul Sandifer’ (Webb and Sutcliffe 1971). (Sandifer had died suddenly, at the early age of 56 years in 1964.)

Kinsbourne felt the contortions seemed to be voluntary trick movements aimed at relief of discomfort. The positions adopted by the children were extraordinary and captured in photographs. As an example, case 2 was a 7-year-old boy: ‘When the boy was standing or lying he would overextend his neck and rotate his head to one or other side. His preferred posture for reading was lying supine on his bed with his head hyperextended over the edge and holding his book above him’. With case 4 there was ‘continuous obtrusive head rolling from side to side along the arc of a circle centred upon the vertical axis of the body. These movements attended all his activities and resulted in the occasional adoption of bizarre postures. Thus, he might sit with his head turned sideways beneath the arm-rest of the chair’.

The five patients were boys aged between 4 and 14 years. They all had a hiatus hernia and associated gastro-oesophageal reflux (GOR) of sufficient severity that all but one had iron deficiency anaemia. The movements were most evident immediately after eating, and were not present in sleep. The bizarre postures upset the parents, but the children seemed untroubled by them. Three of the children said they helped to relieve abdominal discomfort. After successful repair of the hiatus hernia, the movements were completely abolished, and did not reappear.

The initial reports of Sandifer syndrome reflected the patients described by Kinsbourne. For example, a ‘Picture of the Month’ (Gellis and Feingold 1971), showed an emaciated boy adopting a head down posture with rotation to the left in both the lying and standing postures. A similar picture was described in children with GOR, but without an accompanying hiatus hernia (Ramenofsky et al. 1978). With the advent of pH monitoring and other sophisticated techniques for detecting GOR, a less severe clinical picture has been described. Werlin et al. (1980) reported five infants under the age of 8 months, with three less than 17 days of age, who had GOR and abnormal movements. The movements consisted of body shaking or stiffening, at times in association with apnoea. Recently the diagnosis of Sandifer syndrome has been made in a 6-month-old girl who had twisting of the neck to one side that persisted for 7 days, after which the abnormal position moved to the other side (Cafarotti et al. 2014). Feeding seemed to have no relationship with the neck posture. Treatment with ranitidine resulted in a cessation of all symptoms. The clinical picture in these later cases is obviously very different from the original description.

A basic difficulty is that GOR is very common in children especially in infants. It has been estimated that between 30% to 67% of children have GOR (Berman 2015). There are also doubts that pharmacological therapy of GOR is effective (Tighe et al. 2014). Unusual movements are particularly common in young children, as is GOR. If symptoms settle after anti-reflux treatment is given, this does not establish
that GOR was responsible for the symptoms. As discussed above, there are many potentially serious causes of torticollis in children, and the diagnosis of Sandifer syndrome has been considered in children with a retained foreign body in the oesophagus (Smallpiece and Deverall 1982), Chiari malformation (Berthet et al. 2014) and cow’s milk protein allergy (Bamji et al. 2015).

Treatment of Sandifer syndrome obviously involves the expertise of gastroenterological colleagues, but is by no means always straightforward. A 4-year-old boy failed medical therapy and then had laparoscopic fundoplication followed by laparoscopic pyloroplasty, without relief of his abnormal side-to-side head movements (Wasserman et al. 2010). The movements persisted until a naso-jejunal feeding tube was inserted.

Restricting the diagnosis of Sandifer syndrome to children who have pronounced abnormalities of neck movement and posturing, where GOR is severe and is clearly demonstrated to be the cause, is an approach that might be considered. Irrespective of what criteria are used, the diagnosis of Sandifer syndrome should always be made with great caution.

### PAROXYSMAL DYSKINESIAS

The term paroxysmal dyskinesias is particularly applied to three conditions: (1) paroxysmal kinesigenic dyskinesia (PKD); (2) paroxysmal nonkinesigenic dyskinesia (PNKD); and (3) paroxysmal exercise-induced dystonia (PED). Although there are many other conditions where there are recurrent episodes of hyperkinetic movements such as tics, stereotypies, and the episodic ataxias, traditionally these are not considered when paroxysmal dyskinesias are discussed. Paroxysmal dyskinesias are classified as primary where the cause is usually genetic and of dominant inheritance, and secondary when the cause is an identifiable disorder such as hypoparathyroidism or multiple sclerosis.

### HISTORICAL FEATURES

A review of the historical features of the paroxysmal dyskinesias is helpful in understanding the clinical manifestations of the different conditions, and the at times complex terminology and classification systems that have appeared in the literature. To avoid confusion, the current notations PKD, PNKD and PED will be used except when directly quoting from previous papers.

### PAROXYSMAL KINESIGENIC DYSKINESIA

The first known description of paroxysmal dyskinesias was in 1892 by Shuzo Kure of a Japanese man with PKD. (See Ebrahimi-Fakhari et al. 2015 for illustrations from the original paper.) Subsequent reports often regarded PKD as a form of reflex epilepsy. The most detailed of these, and which is beautifully described the clinical features of PKD, was by Lishman et al. (1962, p. 104), where seven patients were described. So precise is their description that it is reproduced it here:

‘The attacks usually begin in childhood and occur frequently. They are constantly precipitated by sudden movement and are more likely to occur after a period of rest. Movement of the legs more often than the arms initiates them. An element of surprise or “startle” seems important. In many cases a state of tension, anxiety or self-consciousness makes them more likely. Conversely, subjective preparation for movement and slow initiation of action tend to reduce or abort them. The attacks themselves consist of tonic spasm which may involve the whole body, but is more commonly localised to the limb in which they start or confined to one side. In three cases the movements had a writhing character reminiscent of torsion spasm. Clonic movements were absent. A sensory aura was not uncommon. Whenever present it began in the limb in which the movement would start and spread briefly before spasm supervened. In any given case the pattern of attack was generally stereotyped, though attacks might be arrested before fully developed. Consciousness was never lost, though in some cases there was evidence of transient clouding. Attacks could sometimes be voluntarily induced, provided the provoking movement was abrupt and forceful.

Lishman et al. (1962) did not give a detailed account of treatment, but phenytoin, when used, seemed to be effective. Phenobarbitone gave variable results.

Kertesz (1967) introduced the term paroxysmal kinesigenic choreoathetosis emphasising the provocation by movement, the short duration of the episodes, the good response to phenytoin and the familial occurrence, but speculated that the inheritance was recessive. (Subsequently it became clear that the inheritance is autosomal dominant with reduced expressivity.) In 1969, Kato and Araki described a 14-year-old girl whose episodes of PKD responded well to carbamazepine, and this has become the most commonly used medication. In 1997, Szepetowski et al. described four families where benign infantile convulsions were inherited as an autosomal dominant trait, together with variably expressed ‘paroxysmal choreoathetosis’. Eight patients had infantile convulsions followed by the later development of choreoathetoid movements. There was strong linkage evidence for the abnormal gene to be present in the pericentromeric region of chromosome 16.

It was long assumed that PKD would be found to be caused by a channelopathy (Berkovic 2000). In 2011, using a combination of exome sequencing and linkage analysis, Chen et al. found that mutations in the gene for proline-rich transmembrane protein 2 (PRRT2) was the cause of PKD.
PAROXYSMAL NONKINESIGENIC DYSKINESIA

In 1940, Mount and Reback described a 23-year-old man with ‘familial paroxysmal choreoathetosis’. The family history stretched back over 100 years to the patient’s great-grandfather, who died at the age of 87. In all, there were 28 affected individuals (18 males and ten females). From the pedigree provided, inheritance was autosomal dominant.

The index patient had both minor and major episodes with the major episodes lasting as long as 2 hours. He found that if he drank a cocktail after dinner, he was certain to have an episode. On days when he drank coffee, tea, alcohol or coca cola, he was more likely to have attacks. Fatigue, concentration and ‘exposure’ also seemed to be precipitating factors. On average he had one ‘large’ and two ‘small’ episodes a day. During the minor incidences he had no difficulty in speaking, but during the large attacks his speech was dysarthric and at times he was anarthric. The large episodes were characterised by choreoathetoid, ballistic and dystonic movements. In a severe episode if he attempted to walk, dancing movements occurred in the lower limbs, sometimes throwing him off balance. There was no alteration of consciousness. He found that the episodes ceased more quickly when he lay down. If he was able to go to sleep, even for a few seconds, the episode was over when he awoke.

In 1968, Richards and Barnett described another large family with PNKD from Canada. They noted that it was a less common condition than PKD, and the two were often confused in the literature. In contrast to paroxysmal kinesigenic choreoathetosis, they suggested it be called paroxysmal dystonic choreoathetosis, or Mount and Reback syndrome. In 2004, Rainer et al. identified missense mutations in the myofibrillogenesis regulator gene (MR-1) in 12 affected individuals in two unrelated PNKD kindreds.

PAROXYSMAL EXERCISE-INDUCED DYSTONIA

In 1977 Lance described two families. The first had the typical features of PNKD. The second family consisted of a man who died at 58 years of age, his then 44-year-old daughter, and her 23-year-old daughter. These individuals developed dystonia which mainly affected the legs after exercise. The dystonia was never precipitated by sudden movement, but by steady exercise such as walking ‘a mile’ (1.6 kilometres). The incidences were also brought on by other forms of exercise, such as a game of tennis or strenuous housework. The 23-year-old woman noted that her episodes started with a sensation of heaviness of the legs and cramping of the feet, followed by inversion of both feet, and writhing movements at the ankles. The duration of exercise required to provoke her episodes was variable. On some days an episode could start after walking only 200 metres, but on other occasions she could walk 8 kilometres without any trouble. The episodes usually lasted between 5 and 30 minutes.

CLASSIFICATION SCHEMES

Lance (1977) discussed these two families and in addition reviewed the literature of PKD, which was clearly the most common form of paroxysmal dyskinesias, as he was able to identify 100 cases. A modified form of his classification scheme can be found in Table 21.1.

Demirkiran and Jankovic (1995) subsequently suggested the generic term paroxysmal dyskinesia replace the previously used choreoathetosis, as the incidences could be choreic, ballistic or dystonic and in some episodes there was more than one movement disorder. They proposed a more complex classification scheme incorporating phenomenology, duration of episodes and aetiology. Psychogenic disorders were included as a secondary cause of PNKD, and some of the clarity provided by the Lance scheme was lost in this attempt to cover all possible presentations. Bruno et al. (2004) included the control of the events by phenytoin or carbamazepine as part of the defining criteria for the diagnosis of PKD.

PAROXYSMAL KINESIGENIC DYSKINESIA

A large number of reports followed the identification of PRRT2 mutations as a cause of PKD by Chen et al. (2011). Ebrahimi-Fakhari et al. (2015) found that 1444 patients with 70 different PRRT2 mutations had been reported over a 4-year period. The vast majority of cases were familial in origin, and almost 80% carried the same c.649dupC frameshift mutation. Ninety-five per cent of patients fell into the diagnostic spectrum of benign familial infantile convulsions, infantile convulsions followed by PKD, or PKD alone.

### Table 21.1 Classification of paroxysmal dyskinesias

<table>
<thead>
<tr>
<th>Form</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Prolonged episodes</strong></td>
<td>2 min–4 hours (PNKD)</td>
</tr>
<tr>
<td><strong>B. Intermediate form</strong></td>
<td>5–30 min (PED) precipitated by continued exertion, not sudden movement</td>
</tr>
<tr>
<td><strong>C. Brief episodes</strong></td>
<td>Seconds–5 min (PKD)</td>
</tr>
<tr>
<td>1 Familial</td>
<td></td>
</tr>
<tr>
<td>2 Sporadic</td>
<td></td>
</tr>
<tr>
<td>a Primary</td>
<td>Lesions of premotor cortex, lesions of basal ganglia, cerebral palsy, multiple sclerosis, hypocalcaemia</td>
</tr>
<tr>
<td>b Secondary (symptomatic)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Lance (1977).
Benign Familial Infantile Convulsions

PRRT2 mutations are also responsible for benign familial convulsions (BFIC). Typically there are afebrile seizures that begin between 3 and 12 months of age, and remit after 1–2 years. Usually there are clusters of focal dyscognitive, or secondarily generalised tonic–clonic seizures. Heron et al. (2012) identified heterozygous mutations in PRRT2, in 14 of 17 families (82%) affected by BFIC, indicating that PRRT2 mutations are the most frequent cause of this disorder. Heron et al. also found PRRT2 mutations in five of six (83%) families affected by infantile convulsions and choreoathetosis (ICCA) syndrome. Steinlein et al. (2012) reported similar results with BFIC. Zara et al. (2013) identified 21 families with 78 individuals affected by BFIC who had PRRT2 mutations. Five individuals from three families developed PKD in childhood or adolescence. Carbamazepine was only used as treatment in a few of the families in these reports. As BFIC is a self-limiting condition, it is difficult to make strong recommendations, but unless there is a risk of Stevens–Johnson syndrome it would seem reasonable to use carbamazepine for BFIC, if treatment seems warranted. Febrile seizures have also been reported in patients with PRRT2 mutations (Marini et al. 2012; Scheffer et al. 2012). In their review Ebrahimi-Fakhari et al. (2015), felt the association of PRRT2 mutations with febrile seizures was ‘more coincidental than causal’.

Other Manifestations of PRRT2 Mutations

PRRT2 mutations have been found to cause some cases of paroxysmal hypnogenic dyskinesia (PHD) (Liu et al. 2016). In this condition there are unprovoked dystonic, choreoathetoid and ballistic episodes during sleep. In the Liu paper, two of five children with typical PHD, with onset of events between 2 months and 3 years, were found to have PRRT2 mutations.

PRRT2 mutations have also been associated with migraine (in particular hemiplegic migraine), ataxia, absence seizures and benign paroxysmal torticollis (Dale et al. 2012; Gardiner et al. 2012; Marini et al. 2012; Riant et al. 2012). There is a report of a boy with a PRRT2 mutation and hemiplegic migraine, whose episodes stopped completely after he was treated with carbamazepine (Dale et al. 2014). It appears that hemiplegic migraine is the most common primary diagnosis in PRRT2 mutation carriers who do not have BFIC or PKD (Ebrahimi-Fakhari et al. 2015).

Homozygous mutations of PRRT2 are associated with a much more severe phenotype. Manifestations include intellectual disability, episodic ataxia, absence seizures and cerebellar atrophy (Najmabadi et al. 2011; Labate et al. 2012; Delcourt et al. 2015). Delcourt et al. (2015) noted that three or more forms of paroxysmal neurological disorder could occur in the same patient, and the episodes tended to persist.

The mechanism by which mutations in PRRT2 cause these various manifestations is unknown. PRRT2 has been shown to interact with the synaptic protein SNAP25 and it seems likely that the problems relate to abnormalities of synaptic neuro-
transmission (Ebrahimi-Fakhari et al. 2015; Gardiner et al. 2015).

Secondary Causes of Paroxysmal Kinesigenic Dyskinesia

There are a number of conditions that have been described as secondary causes of PKD. These include hypoparathyroidism, pseudohypoparathyroidism, birth injury, head injury, multiple sclerosis, hypernatremia, thyrotoxicosis and insulin-dependent diabetes (Nardocci et al. 1989). In a familial case of PKD with the typical features, including immediate cessation of events with carbamazepine, investigations may not be necessary. However, in a sporadic case it seems sensible to organise neuroimaging, and blood tests including measuring calcium, thyroid function tests, and fasting blood glucose level. Other investigations would relate to the clinical setting, as would treatment.

Seizures, in particular those arising from the supplementary motor area, can have similarities to PKD, having both an aura and movement-induced events, in particular limb spasm (Falconer et al. 1963). However, usually there are more unprovoked events than typically are seen in PKD. There may also be secondarily generalised seizures.

PAROXYSMAL NONKINESIGENIC DYSKINESIA

Bruno et al. (2007) published a wonderfully detailed analysis of the clinical features of patients with PNKD with MR-1 mutations. They described 49 patients (27 males and 22 females) from eight kindreds. Neurological examination was normal in all between episodes except for a child with presumably coincidental cerebral palsy. The onset of the events ranged from age 3 months to 12 years (with an average of 4 years). In 16 patients (33%), the episodes started before the age of 1 year. Forty-one per cent of patients reported premontory sensations preceding an episode. In most, this was a sense of stiffening or numbness of a limb, but in 20% it was more a sense of anxiety. The events were most often a combination of dystonia and chorea, but 12% reported dystonia only. Speech involvement occurred in 45% of patients. Less common problems included blepharospasm, risus sardonicus and diplopia at the height of an event. Typical episodes lasted 10 minutes to 1 hour, but this could range from several minutes to 12 hours. Most patients had a period in their life where they were having at least weekly occurrences. With age, the frequency of episodes tended to decrease. Six per cent reported only a small number of events in their life, with one patient only ever having one episode.

Reflecting the initial report, a striking feature was precipitation of episodes after drinking caffeine and alcohol. This was seen in almost all patients. Emotional stress also seemed to lower the threshold for the incidences. In 70% of patients, going to sleep could abort the episode. Contrary to the impression from the previous literature, most patients who took benzodiazepines, either during, or to prevent an episode, felt they were helpful. Headaches, including migraine, were a common additional symptom with these patients. Penetrance of the MR-1 mutation was extremely high, with only one very young patient being asymptomatic.

Bruno et al. (2007) also looked at patients from six other kindreds with PNKD, who were MR-1 mutation-negative. They had a much more variable clinical picture in terms of onset, precipitants, clinical features, and response to medication. Exercise was the most common trigger, reported in 68% of the patients.

There may be multiple different genetic abnormalities responsible for patients with PNKD who are MR-1 mutation-negative. There are two reports of PNKD caused by mutations in KCNMA1 (Du et al. 2005; Zhang et al. 2015), and it is likely other abnormalities will be found in the future. Zorzi et al. (2008) reported three patients with overlapping PNKD and PED phenotypes who had glucose transporter deficiency. All had microcephaly and intellectual disability, and two had seizures, features that are not seen in MR-1 mutation positive patients.

Although the episodes of PNKD can be disruptive to life, they are rarely life-threatening. However, Zittel et al. (2015) reported the case of a MR-1 mutation positive 19-year-old girl, whose mother had died at the age of 37 years from suffocation due to laryngeal dystonia during a PNKD episode. The episodes in this girl did not respond well to clonazepam, but there was a marked improvement when acetazolamide was added. The authors suggested this should be considered early in the treatment of patients with PNKD.

Other medications that have been reported to help in individual cases of PNKD include haloperidol, levetiracetam, valproate and anticholinergics (Mink 2015). Carbamazepine is generally ineffective. There are several reports of adults with PNKD responding to deep brain stimulation of the globus pallidus, but no reports of children.

Episodes of PNKD can be misinterpreted as psychogenic in origin, and as in many movement disorders, there may be associated psychiatric difficulties. This is exemplified by the paper of Walker (1981), who described two siblings who had both come under psychiatric care because of suicide attempts, and were found to be the children of the patient described by Mount and Reback.

PAROXYSMAL EXERCISE-INDUCED DYSTONIA

Twenty years after the initial description by Lance (1977), Bhatia et al. (1997) reported eight new sporadic cases of PED, and reviewed the literature. There were, including their own patients, only 20 cases reported. Five patients came from two families, and the other 15 were sporadic. It was suggested the term ‘paroxysmal exercise-induced dystonia’ be used, rather than dyskinesia as dystonia was the dominant movement disorder.
In 2008, mutations in \textit{SLC2A1}, which encodes GLUT1, the main transporter for glucose across the blood–brain barrier, were found to be a cause of PED. Suls et al. (2008) studied a five-generation family and identified a heterozygous missense mutation in \textit{SLC2A1} in 22 affected family members. Three other nuclear families with a similar phenotype were found to have frameshift and missense mutations in \textit{SLC2A1}. From a total of 25 affected individuals from these four families, 19 had a history of PED (76%), and 14 of epilepsy (56%). In the 19 patients with PED, median age at onset was 8 years with a range of 3–30 years. PED was characterised by choreoathetosis, dystonia, or both, with the legs involved in all patients. In ten patients (55%), only the legs were involved. In six (33%) the legs and arms were involved, but with the legs more affected. In two of these six, there was also facial involvement. In the five-generation family, eight of the 19 individuals had PED without epilepsy.

Suls et al. (2008) found that in their cohort, epileptic seizures appeared mainly as generalised tonic–clonic seizures or absences, with the absences having an onset at around 2 years of age, much earlier than is seen with classic absence seizures. One patient had myoclonic seizures, and two patients also had partial seizures. Most mutation carriers were of average intelligence, or had mild intellectual disability, with no difference between patients with PED alone, and those with epilepsy. Compared to patients with classic GLUT1 deficiency, there was a less pronounced decrease in fasting cerebrospinal fluid (CSF) glucose to serum glucose concentration ratio, reflecting the milder phenotype.

Weber et al. (2008) described a three-generation family with PED due to \textit{SLC2A1} mutations, accompanied by epilepsy, mild developmental delay, reduced CSF glucose levels and haemolytic anaemia. They also screened four other families in whom PED was combined with epilepsy, developmental delay, or migraine, but not with hemolyis, and identified two additional \textit{SLC2A1} mutations. The age at onset of the dyskinesia varied between 10 and 15 years (mean 13 years). Stress, exertion and fasting provoked the appearance of dyskinesia.

Schneider et al. (2009) screened ten patients with PED and found that two had \textit{SLC2A1} mutations. One had previously suffered childhood absence epilepsy and, at the time of review, she also had hemiplegic migraine. The other patient only suffered from PED. The authors proposed that \textit{SLC2A1} mutations can present with a spectrum of severity with microcephaly, intractable seizures, and intellectual disability at one end, and isolated PED at the other. Afawi et al. (2010) described a family with \textit{SLC2A1} mutations, including two members who had PED alone, two with epilepsy alone, and one person who had both. The PED appeared when the patients were between 10 and 15 years of age (mean 13 years), and the onset of epilepsy was between the ages of 13 and 30 years (with a mean of 19 years). The seizures were tonic–clonic in three individuals, and myoclonic with myoclonic status in one.

Ramm-Pettersen et al. (2013) reviewed the response of six patients with \textit{SLC2A1} mutations and PED to dietary treatment. They were mostly adolescents, and three had mild intellectual (disability). In the one patient given the ketogenic diet, the PED episodes stopped. The other were given the modified Atkins diet and, in three, the episodes stopped, but they remained a problem in the two others. Being on the ketogenic diet in particular, but also the modified Atkins diet, is no small undertaking, and in mildly affected patients with PED as their only symptom, a careful discussion of benefit versus risk is obviously important. There is a report of patients with dystonic tremor due \textit{SLC2A1} mutations refusing treatment with either the ketogenic diet, or antiepileptic drugs (Roubergue et al. 2011).

In patients with PED, the presence of seizures strongly raises the possibility that \textit{SLC2A1} mutations are the underlying cause. The seizures may have an early onset, or be delayed until adolescence, and be relatively mild. (A more detailed discussion of glucose transporter deficiency can be found in the Treatable Movement Disorders Section in Chapter 19.)

PED appears to be a heterogeneous condition. Multiple other causes have been identified besides \textit{SLC2A1} mutations. These include a mother and son where PED was due to GTP cyclohydrolase deficiency (Dale et al. 2010), early-onset Parkinsonism in adults (Bozi and Bhatia 2003), moyamoya disease (Lyoo et al. 2007), pyruvate dehydrogenase deficiency in a girl who responded to thiamine therapy (Castiglioni et al. 2015) and an \textit{ECHS1} mutation in a 15-year-old girl who had mild pallidal changes on MRI (Olgiati et al. 2016). Other causes will no doubt be found in the future.

**APPROACH TO PAROXYSMAL DYSKINESIAS**

Although paroxysmal dyskinesias can be a confusing subject, the approach suggested by Lance provides a very useful starting point. If the patient has short-lived attacks, often provoked by sudden movement, then PKD is likely. If the attacks are dystonic, affect particularly the legs, last longer and come on after sustained exercise, then PED is the probable diagnosis. When there are prolonged episodes, then PNKD needs to be considered, especially when the episodes are provoked by the consumption of caffeine or alcohol.

**PSYCHOGENIC PAROXYSMAL DISORDERS**

The huge topic of psychogenic disorders is discussed in Chapter 32. The following from Kinsbourne (1964, p. 1058) illustrates some of the difficulties. ‘When a patient presents with a disorder of movement and posture, it is natural in the first instance to think of neurological disease, such as of the basal ganglia. If the clinical features are not those of a recognised neurological syndrome, the possibility of a psychogenic disorder may then arise. But sometimes both these explanations prove incorrect.’
REFERENCES


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PART IX

Disorders of the Oculomotor, Visual, Auditory and Vestibular Systems

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Disorders of Visual and Oculomotor Functions

Carey Matsuba

Disorders of Visual Function

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    Toxic and Nutritional Optic Neuropathies
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    Inherited Retinal Diseases
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Combined Ophthalmoplegias 1140
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Congenital IIIrd Nerve Palsy 1141
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Disorders of Visual and Oculomotor Functions

Carey Matsuba

The visual system plays an important role in the exploration and analysis of the external world. Proper functioning of this system requires the integrity of an extremely complex neural network easily disturbed by a vast number of central nervous system (CNS) disorders, making it important to review this system through the components from ocular structures to the retinal transmission of the visual information through the optic nerve to the occipital cortex. This transmission can be impeded or disturbed by many pathological processes that may in turn influence oculomotor function. Clinical and electrophysiological analysis of the visual system disorders is a sensitive means of exploring the CNS function and abnormalities of oculomotor movements and constitutes an essential part of the neurological examination.

DISORDERS OF VISUAL FUNCTION

VISUAL IMPAIRMENT
OVERVIEW AND DEFINITIONS

Visual impairment has historically been defined by two features: a reduction in visual acuity and/or loss in visual field. The World Health Organization defines visual impairment as seen in Table 22.1, however, the definition has particular challenges in the paediatric population. The primary challenge is that in young children vision function changes with maturity and therefore there are no standard criteria for childhood visual impairment. In addition, the measurement of visual acuity and visual fields in children can be challenging to the clinician. Many children with a visual impairment may go undiagnosed for this reason while for others nonocular causes of a reduction in visual acuity or field loss are occasionally not considered in the realm of visual impairment. In ICD-10 neurological causes of a reduction in visual acuity or loss in visual field are not explicitly included in the aetiologies of a visual impairment. Both of these conditions would be coded generically as H54.7 (Table 22.2).

It should be noted that this traditional definition of visual impairment differs from problems with visual function. All too often children with developmental difficulties may be incorrectly diagnosed as having a visual impairment, such as children with reading disorders or poor visual-motor coordination. Alternatively, some children may have colour blindness or lack of stereopsis. Although physiologically these are common visual dysfunctions, these conditions alone do not meet the criteria of visual impairment.

Despite limitations in diagnosis and problems with definition, the aetiology of visual impairment encompasses multiple conditions which can occur in isolation or in conjunction with a systemic condition. Estimates of prevalence greatly vary, in part related to the difficulties in diagnostic criteria and challenges with assessment; in developed countries about one or two out of 1000 children will meet the criteria of visual impairment (Gilbert et al. 1999). The age at diagnosis of visual impairment varies depending upon the underlying aetiology, presence of co-existing conditions and access to appropriate assessments. Most children with visual impairment should theoretically be identified early, as the most common causes of visual impairment are present in the first year of life. For example, cortical visual impairment, the most common aetiological condition, has been associated with perinatal injury, structural brain anomalies and metabolic disturbances. Similarly, the most common optic nerve disease leading to visual impairment, optic nerve hypoplasia, as well as structural eye diseases, can be typically identified in the first days to months of life: the typical presentation not only involves challenges with visual attention but also comorbid health and neurodevelopmental difficulties. The combination of abnormalities leads to the earlier detection of most conditions leading to visual impairment: given this early presentation there are no systematic screening programmes for visual impairment.
visual capabilities of the child increase to adult levels. Atkinson 2000; Kiorpes and Movshon 2004): as this occurs the brain continues well after this event (Magoon and Robb 1981; Mrosovsky 1989). At birth the myelination of the optic nerve fibres and the occipital cortex is incomplete. This division is important as anterior pathway comprising of the eye and optic nerve as well as the posterior pathway comprising of the optic radiations and occipital cortex. Any abnormality within the pathway can lead to a reduction in visual acuity and/or visual field loss. It is important to note that this chapter focuses on causes of visual impairment.

The visual pathways are an intricate organised system. The visual pathway comprises the eye, optic nerve, optic radiations and occipital cortex. Any abnormality within the pathway can lead to a reduction in visual acuity and/or visual field loss. It is important to note that this chapter focuses on causes of visual impairment. The visual pathways are an intricate organised system. The visual pathway comprises the eye, optic nerve, optic radiations and occipital cortex. Any abnormality within the pathway can lead to a reduction in visual acuity and/or visual field loss. It is important to note that this chapter focuses on causes of visual impairment.

The individual conditions that lead to visual impairment are uncommon, many being associated with systemic disorders meaning that careful history taking and examination are needed. This evaluation goes beyond a full ophthalmological assessment.

Assessment of children with suspected visual impairment primarily relies on history and observation. Although the child with visual impairment may present at any age, the majority of aetiological causes stem from genetic, prenatal or perinatal causes. Patients with visual impairment are more likely than not to have additional health and neurodevelopmental conditions meaning that particular focus on a complete neurological and developmental history is important.

When observing visual clinical signs, those such as light sensitivity or exotropia can help guide clinicians to possible aetiological causes. Photophobia may indicate a cone disorder, corneal dystrophy or glaucoma while exotropia may be a sign of visual inattention, often present in cortical visual impairment. Clinicians should use the time during information gathering to intermittently observe visual function, including visual behaviours such as head tilt, visual working distance at play: head tilt may indicate the presence of nystagmus, field loss or a problem with the extraocular muscles. In addition to eye alignment and the presence of nystagmus, craniofacial anomalies and pigmentation abnormalities can also be used to assist with diagnostic profile.

### Ophthalmological Assessment for the Non-Ophthalmologist

The ophthalmological assessment is a key component in the evaluation of visual impairment. A full ophthalmological examination includes a fundoscopic examination, evaluation of visual acuity and visual field testing however such examinations can be difficult in infants, young children and children with developmental disabilities. The assessment should also include identification of the reflex responses such as pupillary light reflex, which is reliably present after 31 weeks of gestation: a blink response to light develops at approximately the same period (dazzle reflex) but a blink to threat is unreliable and late in appearance. Fixation and following are present from very early in life: infants turn their head towards a

---

**Table 22.1 World Health Organization classification of levels of visual impairment**

<table>
<thead>
<tr>
<th>Category</th>
<th>Visual acuity under best correction</th>
<th>Central visual field*</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/18 6/60 3/10 20/70</td>
<td>Low vision</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6/60 3/60 1/10 20/200</td>
<td>Low vision</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3/60 (count finger @ 1m) 1/20 20/400</td>
<td>&lt;5 de&lt;10 deg</td>
<td>Blind</td>
</tr>
<tr>
<td>4</td>
<td>1/60 1/50 20/1200</td>
<td>&gt;5 de&lt;10 deg</td>
<td>Blind</td>
</tr>
<tr>
<td>5</td>
<td>No light perception</td>
<td>Blind</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Undetermined or unspecified</td>
<td>Low vision</td>
<td></td>
</tr>
</tbody>
</table>

*Visual field restriction criteria applicable even if visual acuity is better than for that category.

**Table 22.2 ICD-10 classification of visual impairment**

<table>
<thead>
<tr>
<th>ICD code</th>
<th>Level of visual impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H54.0</td>
<td>Blindness in both eyes</td>
</tr>
<tr>
<td></td>
<td>Visual impairment categories 3, 4, 5</td>
</tr>
<tr>
<td>H54.1</td>
<td>Blindness in one eye, low vision in other eye</td>
</tr>
<tr>
<td>H54.2</td>
<td>Low vision in both eyes</td>
</tr>
<tr>
<td>H54.3</td>
<td>Unqualified vision loss in both eyes</td>
</tr>
<tr>
<td></td>
<td>Visual impairment categories 9 in both eyes</td>
</tr>
<tr>
<td>H54.4</td>
<td>Blindness in one eye</td>
</tr>
<tr>
<td>H54.5</td>
<td>Low vision in one eye</td>
</tr>
<tr>
<td>H54.6</td>
<td>Unqualified vision loss in one eye</td>
</tr>
<tr>
<td>H54.7</td>
<td>Unspecified vision loss</td>
</tr>
</tbody>
</table>

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**THE VISUAL PATHWAY**

The visual pathway comprises the eye, optic nerve, optic radiations and occipital cortex. Any abnormality within the pathway can lead to a reduction in visual acuity and/or visual field loss. It is important to note that this chapter focuses on conditions causing a non-reversible reduction in visual acuity or loss in visual field and hence common ophthalmological issues such as refractive error, strabismus and colour vision abnormalities are not specifically discussed, however these conditions are often present in conjunction with aetiological causes of visual impairment.

The visual pathways are an intricate organised system. Often the systems are divided into two areas, the anterior pathway comprising of the eye and optic nerve as well as the posterior pathway comprising of the optic radiations and occipital cortex. This division is important as anterior pathway conditions can be directly visible by ophthalmological evaluation, whereas the posterior pathway is hidden. In many conditions there can be aberrations in both pathways.

Visual function relies on the combined development of the eye and brain. Although structurally the eye is formed at the time of birth the myelination of the optic nerve fibres and brain continues well after this event (Magoon and Robb 1981; Atkinson 2000; Kiorpes and Movshon 2004); as this occurs visual capabilities of the child increase to adult levels.

**CLINICAL ASSESSMENT OF VISUAL IMPAIRMENT**

The individual conditions that lead to visual impairment are uncommon, many being associated with systemic disorders...
diffuse light from a few days of age. The human face, at a distance of approximately 30 cm is the best target for fixation: following in the vertical plane is particularly useful as vertical eye movements are not normally random movements and are, therefore, more reliable than horizontal ones. Nystagmus induced by rotation about the body axis is present in healthy term infants but inhibited within a few seconds by visual fixation, whereas in blind children it may persist for 15 seconds.

The ocular assessment should include inspection of the eye for structural anomalies such as size, presence of coloboma or presence of nystagmus. Extraocular movements are an important component to be assessed: typically extraocular muscles are assessed through alignment. Pupillary responses give a dynamic evaluation of the system and can identify abnormalities in the visual pathways as well as significant differences between the left and right visual pathways.

Stereopsis can be used as a measure of eye alignment but unfortunately can only be measured in children developmentally 2–3 years of age. When measuring stereopsis it is important not to dissociate the child's vision: dissociation can occur when the examiner covers one eye, breaking stereovision meaning that testing for stereopsis should be undertaken first using one of several common tests such as the Lang stereo tests or two pencil test. When a child is not able to perform a stereo testing there are several measures of alignment including simple inspection, the Bruckner's test, as well as cover and uncover test: the Bruckner's test (http://www.ophthbooook.com/wpcontent/uploads/2007/12/ped-hirchburg.jp) is a simple light reflex test as is the Cover and Uncover test (http://www.aafp.org/afp/1998/0901/afp19980901p691-f5.jpg).

Fundoscopic evaluation may be the most difficult to perform on a child as well as to evaluate for a non-ophtalmologist clinician. Subtle changes particularly in the periphery require indirect ophthalmoscopic evaluation. For the experienced clinician most children will be able to cooperate for direct ophthalmoscopic examination with the assistance of a fixation target. Although a thorough indirect fundoscopic evaluation is often needed, the non-ophtalmologist clinician requires a review of the macula and optic disc.

Refractive errors are common in children with neurological impairments. In the non-verbal or young child refraction can be performed by an ophthalmologist through cycloplegic retinoscopy. The ophthalmologist uses the retinoscope to shine light into the child's dilated eye and observes the reflection (reflex) off the patient's retina. While moving the light across the dilated pupil the ophthalmologist observes the relative movement of the reflex and then uses a phoropter or manually places lenses over the eye (using a trial frame and trial lenses) to 'neutralise' the reflex: in this way a refractive error can be measured. Depending on the symptoms such as the presence of strabismus the child could be placed in corrective lenses, optimising their vision.

**Visual Acuity Measurements**

Visual acuity is a measure of one's ability to see detail. It is a useful measure of total visual pathway function and improves in childhood. At birth, the macula is immature but with time matures during infancy. It is measured by several standard conventions such as 20/20 or 6/6 (Snellen), 1.0 (decimal) or 0.0 logMAR. In practice these measures all relate to a standard based on the comparison of standard visual acuity compared to the individual’s measured acuity. Most clinicians are familiar with matching acuity charts at 20 feet or 6 metres.

There are a number of visual acuity tests that can be used in children including the BUST visual acuity test card, commonly used by the neurologist, however, the use of the near test must be used with some caution. For example, the BUST card uses numbers, meaning that a child would have to be familiar with such units to perform the test. Most early visual acuity tests rely on matching figures such as the HOTV, tumbling E or picture tests. At developmental age 3 years children have started to match and therefore acuity testing could be tried (American Academy of Pediatrics et al. 2003).

In young children estimates of visual acuity are available using preferential looking acuities or electrophysiological procedures (visual evoked potentials) as they may not be able to perform standard matching acuity charts. Visual evoked potential measures have been shown to record better visual acuity measures over preferential looking acuities (Mayer et al. 1995; Salomao and Ventura 1995). Both measures have been normalised in infants and young children, although visual evoked potentials measures tend to report higher acuities than Preferential looking acuities particularly in younger children. This is partially related to higher processing required with visual attention and eye-head coordination in the behavioural testing (Braddock and Atkinson 1988). Similarly, in children with cognitive difficulties letter acuities have been found less than preferential looking acuities (Mayer et al. 1983; Friedman et al. 2002).

**Visual Field Measurement**

As with visual acuity, visual fields mature with time. Term infants have significantly smaller visual fields than older children (Schwartt et al. 1987; Mayer and Fulton 1994), with the visual field increasing through infancy to 4 years: by 18 months of age it can be as large as 90–95% of that in adults. Visual fields are an important measure of visual function however formal visual field measurements are difficult in young children. In these children estimations of the visual field can be done by confrontation which can be performed by presenting secondary targets in the child’s periphery, while the child is fixating on a primary fixation target, typically the examiner’s face. By observing the orientating response with either head or eye movements a clinician can get an estimation of peripheral field while spurious results can also occur, resulting from other distracting movements. To adjust a wand with a fixation target or light at the end can be used to minimise errors. This technique is not particularly accurate for scotoma or subtle changes in the extremes of the peripheral field, but it can get an estimation of a hemi or quadrantanopia, with these field deficits being relatively the most common presenting condition of field loss. With maturity a Goldmann kinetic perimetry can be performed in children as young as 4 years (Mayer and Fulton 2005).
Additional testing for the non-ophthalmologist

There are many electrophysiological measures to assess vision and non-ophthalmology clinicians should be familiar with some, such as the electro-oculogram (EOG) used to assess maculopathy primarily due to retinal pigment epitheliopathy. Maculopathies in paediatrics are relatively uncommon. The electroretinogram (ERG) is used to identify cone and rod dysfunction and can be used to assist or confirm the diagnosis of many retinal diseases. Optical coherence tomography (OCT) is an important non-invasive, imaging technique that allows cross-sectional and three dimensional measurements of the retina.

The visual evoked response to flashes is an excellent technique to demonstrate the integrity of the visual pathway without patient cooperation (Baker et al. 1995). A positive cortical wave with a peak latency of 300ms is first demonstrable at 30 weeks' gestation with the latency then declining by about 10ms each week through the last 10 weeks of gestation (Taylor et al. 1987; Leaf et al. 1995). By about 3 months of age the morphology and latency of the visual evoked responses are relatively mature, but the interpretation of the responses at earlier periods remains difficult. Visual evoked procedures, such as patterns, shifting orientation and sweep are being used that can provide greater information regarding the visual axis.

For central causes of vision loss neuroimaging techniques may be useful in the assessment of children with visual impairment (Flodmark et al. 1990) as they can detect associated cerebral malformations such as structural anomalies along the visual pathways.

Management of visual impairment

Once the clinician has diagnosed a visual impairment it is important to consider appropriate management strategies, however, many clinical diagnoses are descriptors of a phenotype. For example, retinitis pigmentosa is an inherited condition caused by mutations occurring in one of several genes which may be clinically indistinguishable. But genetic testing has become more prominent in the investigation of ophthalmological conditions as newer experimental treatments, such as gene therapy, are being studied, seen in Leber's congenital amaurosis (Bainbridge et al. 2008), however, the mainstay of treatment is supportive.

By definition visual impairment is a non-reversible reduction in visual acuity or loss in visual field. It is important to optimise the vision, particularly in regards to refractive error. In many circumstances environmental adaptations, including preferential seating, magnification and optimal lighting, can help with functional vision. In addition, many conditions have associated comorbid health issues. Optimising the health of a child with visual impairment may improve their visual function, the most apparent form of which would be the treatment of refractory seizures.

Following the diagnosis of a visual impairment referral to vision support services early is important, if available. Specialised services can offer information on the condition and disability, with primary caregivers the leads in providing support to the child. Through the assistance of specialised services and/or local and national support groups, developmental, educational, social and cultural issues can be addressed.

The habilitation of children with visual impairment results from skilled, early intervention. As children with visual impairment are at risk of developmental impairments, assessing and supporting all domains of development are important. Often children are best supported through a multidisciplinary team which may include ophthalmologists, paediatricians, neurologists, geneticists, nurses, psychologists, speech-language pathologists, audiologists, physical therapists, occupational therapists, assistive technology specialists, educators as well as orientation and mobility specialists.

There are a number of points to consider in the habilitation of children with visual impairment, the first being to optimise and/or promote vision development. Encouraging visual interaction with the environment can be reduced by severe acuity or field loss, defective eye movements, marked developmental delay or visual attention disorders. When some vision is present opportunities to encourage vision should be undertaken immediately. Initially the presentation of meaningful but simply designed targets should occur: with time and better responses more complex figures can be used. Typically the presentation should be done at a close range often using concrete objects.

Early intervention providers, school educators, technology specialists and mobility specialists are important in the habilitation of children with visual impairment, with these trained individuals planning the curricula and teaching the children. The curriculum includes typical learning objectives but greater detail is needed for concept formation, orientation and mobility, daily living techniques, nonvisual communication in reading, writing, speaking, listening and the use of technical aids. These professionals are also important in explaining the educational environment as impaired accommodation, contrast sensitivity, colour perception, lighting, or eye movements can adversely affect learning. When the visual disorder is progressive the rate of deterioration determines the timing of introduction of Braille and assistive devices. Low vision aids and assistive technologies are more effective when educators are involved in the transition and instructions.

It is beneficial to introduce these services early so children with visual impairment have opportunities to become accustomed to these supports. Older children will benefit from low vision clinics operated by ophthalmologists or optometrists which provide continuity, particularly with low vision aids and technology.

Vision screening

Paediatric vision screening is primarily used to identify refractive error, strabismus and amblyopia. Amblyopia is clinically defined as a significant reduction in visual acuity, despite appropriate correction of a refractive error (Friendly 1987) and is the most common cause of unilateral vision loss.
Typically the examination reveals factors that lead to amblyopia such as anisometropia, strabismus, monocular form deprivation or a combination of these. Unlike many causes of vision loss amblyopia can be treated, leading to improvements in visual acuity, however, vision screening is not used to identify visual impairment.

AETIOLOGIES OF VISUAL IMPAIRMENT

There are vast number of CNS, optic nerve, retinal, and ocular structural disorders that lead to dysfunction of the visual pathways and are often associated with a number of systemic and neurological diseases. The following paragraphs discuss some common conditions that result in a loss of visual field or visual acuity, with the main causes of visual impairment in childhood listed in Table 22.3.

VISUAL IMPAIRMENT DUE TO CNS CONDITIONS

Cortical Visual Impairment

In adults the term cortical blindness describes the complete vision loss due to bilateral damage to the occipital cortex. However, children who present with damage to the occipital cortex differ from adults, leading to the introduction of the term cortical visual impairment (CVI) due to these children often having partial vision loss (Jan et al. 1987). In the mid-1980s this form of visual impairment was being increasingly identified (Whiting et al. 1985; Roland et al. 1986). The term CVI applies to a reduction in visual acuity due to damage of the occipital cortices, in particular the calcarine cortex. In some children the reduction in visual acuity may primarily result from deep subcortical white matter insults such as periventricular leukomalacia meaning that the term cerebral visual impairment has been commonly used as it is more inclusive.

The early diagnosis of CVI remains essentially clinical with supportive investigations. Children may undergo multiple investigations but the results must be interpreted with caution: visual evoked responses may be deceptive as they may be normal despite profound vision loss (Taylor and McCulloch 1991; Wong 1991). An extinguished ERG can be helpful but may be absent in blindness not due to involvement of the retinal sensory epithelium. Study of optokinetic nystagmus may be helpful for the diagnosis of malingering if special equipment is available but clinical assessment is usually the best option.

CVI is now the most common cause of visual acuity loss in young children in developed countries. Traditionally CVI has been defined as a reduction in visual acuity and/or visual field, however, it has also been used to describe eye movement abnormalities and poor visual attention (Weiss et al. 2001). In the presence of acuity loss it is associated with significant comorbidities including cognitive and motor impairments with causes typically including perinatal hypoxic-ischaemia, especially in preterm infants with periventricular leukomalacia (Ng et al. 1989; Lanzi et al. 1998), infections, hydrocephalus, trauma and structural brain anomalies. Rarer aetiologies include hypoglycaemia, seizures, as well as inflammatory and neurodegenerative conditions. Fortunately, unlike in adults, children with vision loss due to occipital cortex injury often have improvement in their visual acuity over time (Roland et al. 1986).

The underlying neurological structural abnormality varies, often dependent upon the onset of the injury, preterm versus term as well as type of injury. In preterm children the most common site of injury is to the periventricular white matter. Often, white matter disease can be divided into hypoperfusion and haemorrhagic while profound hypotensive injuries in preterm children may lead to deep grey matter and brainstem injuries. In term children watershed areas are affected, more likely to occur in the frontal and parietal-occipital regions.
Acquired CVI is frequent in children with some degree of vision usually preserved. Many children present with puzzling visual behaviour and can be shown to have field and/or agnostic deficits including difficulties with recognition, orientation and depth, movement and simultaneous perception (Jan et al. 1987; Jan 1993). CVI may be transient or lasting, with transient CVI frequent following head trauma (Eldridge and Punt 1988) which may be a manifestation of epilepsy, migraine or other acute conditions (Barnet et al. 1970) such as hypoglycaemia (Garty et al. 1987).

Lasting acquired CVI can be a complication of infections especially purulent meningitis or herpes encephalitis, of acute hypoxia following vascular collapse, acute dehydration or status epilepticus (Arroyo et al. 1985; Connolly et al. 1991) as a result of infarction in the territory of both posterior cerebral arteries due to their compression while crossing the tentorial edge. Extensive cortical malformations are a less frequent cause (Jan 1993).

The clinical assessment of children with CVI may be difficult. Patients with CVI often have a normal fundoscopic examination with the optic nerve occasionally having some signs of pallor which would be consistent with transsynaptic degeneration of the geniculostriate pathways, occurring in post natal injuries (Jindahra et al. 2009). However, the optic nerve atrophy is not the major cause of a reduction in visual acuity when found. Nystagmus may be present in conjunction with periventricular leukomalacia while strabismus is a common feature.

Visual acuity measurements may be difficult. Often, the use of forced-choice preferential looking acuities may be able to yield estimates of visual acuities while other tools such as Vernier VEPs may be a reliable physiological measure of visual acuities. Although there may be complete loss of vision lasting weeks or months most patients recover some degree of vision (Lambert et al. 1987; Matsuba and Jan 2006). Even though permanent field deficits and low acuity almost always persist, children appear to have greater recovery of visual acuity compared with adults (Matsuba and Jan 2006; Malkowicz et al. 2006; Werth 2008). The clinical features of CVI often make recognition and/or behavioural manifestations and it is occasionally difficult to distinguish CVI from optic ataxia or dyskinetic eye movements where major disturbances in reaching for objects easily suggest blindness (Perenin and Vighetto 1988; Jan et al. 2001).

Until recently there have been no specific treatments for CVI. With the advent of neuroprotective strategies in the neonatal period there is some hope on the horizon, with cerebral hypothermia possibly leading to neuroprotection following neonatal encephalopathy (Gluckman et al. 2005; Azzopardi et al. 2009). Other neuroprotective medications are also being considered but the effect on CVI is still unknown.

**Development of Ventral and Dorsal Visual Pathways**

Vision influences many areas of child development. In the neonatal period, infants develop visual attention. Once attention is developed, the infant will begin to reach to interact with near objects. Subsequently, vision encourages children to explore more distant objects through visuomotor skills. The complex visual and environmental interaction is influenced by multiple comprehensive visual modules with these modules separated into two main cortical pathways, the dorsal and ventral streams (Milner and Goodale 1995). The ventral stream links the occipital and temporal lobes with connections associated with recognition of geometric forms, route finding and visual memory. The dorsal stream runs between the occipital and parietal lobes, subserving the ability to process the whole visual scene: it is mostly concerned with the perception of movement and visuomotor performance.

Interference with these pathways does not necessarily include a reduction in visual acuity or field but can have functional consequences (Goodale and Westwood 2004). It is thought that children with preferential ventral pathway involvement may have difficulties in recognition of objects in the presence of normal visual acuity, while children with damage to the dorsal stream were also found to have an impaired ability to make accurate visually guided movements (Dutton et al. 2004). Dorsal stream vulnerability has been suggested in children with Williams syndrome (Atkinson et al. 2001): given the complexity of these perceptual difficulties, a more complete systematic evaluation may be useful (Dutton et al. 2010).

**Delayed Visual Maturation**

A healthy term infant typically starts the smiling response at 5 weeks of age followed by the ability to fix and follow at 8 weeks of age. However, some children without a known physiological reason fail to demonstrate these skills, which has led to the term delayed visual maturation (DVM) (Illingworth 1961). There are potentially multiple reasons for this presentation, as most infants with normal ophthalmological and neurological examinations often have a rapid development of normal visual responses. However, DVM is associated with comorbid health and cognitive impairments. In a follow-up study children with a history of DVM often developed normal acuities but over half had a neurodevelopmental impairment (Hoyt 2004).

**VISUAL IMPAIRMENT DUE TO OPTIC PATHWAY DISORDERS**

**Optic Nerve Hypoplasia**

Optic nerve hypoplasia (ONH) is the most common disc anomaly (Table 22.4). It is a developmental defect in the number of optic nerve fibres which may be unilateral or bilateral and may occur as an isolated defect or be associated with other CNS defects, the most common of which is the absence of the septum pellucidum in septo-optic dysplasia (de Morsier syndrome). There are many systemic and teratogenic associations...
Table 22.4  Main causes of optic neuropathies

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td><strong>Developmental lesions</strong></td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
</tr>
<tr>
<td>Septo-optic dysplasia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Heredodegenerative neuropathies</strong></td>
</tr>
<tr>
<td>Dominant optic neuropathy</td>
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<tr>
<td>Leber hereditary optic neuropathy—Behr syndrome</td>
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<tr>
<td>Costeff syndrome (3-methylglutaconic aciduria)</td>
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<td></td>
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<tr>
<td><strong>Metabolic diseases</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Mitochondrial diseases</td>
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<tr>
<td>including Leigh syndrome</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Infantile neuroaxonal dystrophy</td>
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<tr>
<td></td>
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<tr>
<td><strong>Ischaemic neuropathies</strong></td>
</tr>
<tr>
<td>Thrombosis and emboli of retinal arteries</td>
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<tr>
<td>Inflammatory arterial diseases (e.g. panarteritis nodosa)</td>
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<tr>
<td>Venous thrombosis</td>
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<tr>
<td></td>
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<tr>
<td><strong>Compression neuropathies</strong></td>
</tr>
<tr>
<td>Sellar and perisellar tumours</td>
</tr>
<tr>
<td>Meningeal carcinomatosis</td>
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<tr>
<td>Leukaemia and lymphomas</td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory demyelinating neuropathies</strong></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
</tr>
<tr>
<td>Schilder disease</td>
</tr>
<tr>
<td>Postviral neuropathies</td>
</tr>
<tr>
<td>(measles, mumps, chicken pox, infectious mononucleosis, etc.)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Toxic and nutritional neuropathies</strong></td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Other exogenous toxins</td>
</tr>
<tr>
<td>Protein–caloric malnutrition</td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Neighbouring inflammatory lesions</strong></td>
</tr>
<tr>
<td>Sinusitis and ethmoiditis</td>
</tr>
<tr>
<td>Acute purulent and subacute meningitides</td>
</tr>
<tr>
<td>Intraorbital pseudotumour</td>
</tr>
<tr>
<td>Cavernous sinus lesions</td>
</tr>
</tbody>
</table>

ONH is associated with a host of additional conditions. Endocrinological abnormalities related to defective development of diencephalic derivatives are commonly present while infants may have hypoglycaemia in the neonatal period, caused by hypopituitarism, which may lead to seizures. Emergency treatment from the lack of growth hormone is needed in order to avoid sequelae, particularly resulting from the profound hypoglycaemia. The central endocrinopathies can occur in isolation, typically growth hormone deficiency, or in combination affecting both anterior and posterior pituitary glands. Puberty may be precocious or delayed (Hanna 1989).

An early diagnosis of associated cerebral abnormalities is essential considering the endocrinopathies. CT or MRI permits not only the diagnosis of ONH but also the presence of other CNS congenital anomalies such as an arachnoid cyst, hemispheric migrational anomalies, or perinatal injury (Brodsky and Glaser 1993), with the occurrence of bilateral porencephaly or schizencephaly rarely (Menezes et al. 1988).

Neurological deficits can occur in association with ONH. In the presence of structural lesions including thinning or agenesis of the corpus callosum children often have neurodevelopmental problems. Unilateral ONH does not preclude intracranial malformations (Brodsky and Glaser 1993).

Several mechanisms may lead to the formation of ONH, with the condition attributed to a failure of retinal ganglion cell differentiation at 4–6 weeks' gestation. In animal studies deletion of netrin-1, an axon guidance molecule, led to ONH and other CNS migrational anomalies such as agenesis of the corpus callosum (Denier et al. 1997; Oster and Stretavan 2003). Alternatively CNS injuries that occur at the time of
development may lead to failure of the axons to develop. In this process toxins or associated CNS injury may be implicated, leading to a loss of neurons. There are many conditions that have been associated with ONH-including chromosomal disorders such as trisomy 18 and chromosome 13q-, craniofacial anomalies including Aper’s syndrome and Goldenhar syndrome as well as fetal alcohol syndrome.

Although rare, individuals have been reported to inherit ONH (Hackenbruch et al. 1975; Benner et al. 1990). The HESX 1 gene was isolated in two siblings with ONH, absence of the corpus callosum and pituitary hypoplasia (Dattani et al. 1998). It has also been found as a sporadic mutation (Dattani et al. 2000) and may be accompanied by other homeobox genes such as SIX3 and SIX6 or mutations in the PAX6 gene (Azuma et al. 2003; Bennett 2003).

Other Disc Abnormalities

Some disc abnormalities may interfere with vision or be associated with neurological abnormalities of which they may be the presenting manifestation.

Coloboma of the optic nerve may lead to a visual impairment. Despite the appearance it may be difficult to predict the level of vision (Brodsky 1994) which can occur in isolation or in combination with involvement of the retina, iris, ciliary body and choroid. Typically, coloboma of the optic disc may be isolated inferiorly, appearing as a deep excavation with abnormal emergence of the retinal vessels. Coloboma may be unilateral or bilateral. The condition often occurs as part of the CHARGE (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of Growth and development, and Ear abnormalities and deafness), Walker-Warburg and Goldenhar syndromes while the coloboma may be associated with CNS abnormalities which include agenesis of the corpus callosum, in isolation, or as a component of Aicardi syndrome (Chevrie and Aicardi 1986; Aicardi et al. 1987). Isolated cases are sometimes transmitted as an autosomal dominant trait (Savell and Cook 1976). The visual acuity is variable, dependent upon the integrity of the papillomacular bundle.

The morning glory disc anomaly is a congenital, funnel-shaped excavation of the posterior fundus. The disc is enlarged with a white excavated centre, surrounded by an annulus of choriretinal pigmentation changes. Retinal vessels emerge at the margins of the disc and appear to be increased in number, while the macula may be incorporated into the excavation. Most cases are unilateral (Steinkuller 1980) with visual acuity typically suboptimal, ranging from 20/200 to finger counting. In some individuals there appears to be an association with CNS abnormalities, especially trans-sphenoidal basal encephalocele. Other associated brain anomalies include agenesis of the corpus callosum and posterior dilatation of the lateral ventricles (Pollock 1987). Patients with this anomaly need to have ongoing ophthalmological follow-up as there is a risk of serious retinal detachment or retinal tears.

Optic disc drusen are cystic formations buried in the head of the optic nerve whose precise mechanism of formation is not known but which may be transmitted as an autosomal dominant trait with variable penetrance. Drusen present in children as a swelling of the optic disc that may mimic papilloedema (Santavuori and Erkki 1976; Katz et al. 1988) and may occur as an isolated abnormality or be associated with various neurological dysfunctions (Santavuori and Erkki 1976). In adult patients they present at fundoscopic examination as polylubulated cystic formations of distinctive appearance whereas in children they remain buried within the optic nerve head (Fig. 22.2). Therefore, examination of both parents is indicated for any child with pseudopapilloedema as the presence of typical drusen in one of them is of diagnostic importance. Clinically, optic disc drusen develop visual field deficits and on rare occasions central acuity may be lost (Brodsky et al. 1996).

Congenital/Hereditary Optic Nerve Atrophy

Congenital optic nerve atrophy is a relatively common finding in children with neurological disorders. It occurs in most children as a sporadic phenomenon and does not have a high degree of specificity, as it is observed in a number of apparently heterogeneous congenital non-progressive encephalopathies as well as in some early progressive encephalopathies.

Congenital optic nerve atrophy is rarely isolated and often represents part of more complex syndromes that also involve the CNS. Many individuals are affected because of infectious fetopathies such as that caused by rubella virus, brain malformations, sequelae of hypoxic-ischaemic encephalopathy (probably the most common cause) or disorders such as osteopetrosis. In addition there are several hereditary forms which are variably expressed.

Leber hereditary optic neuropathy (LHON) is the most frequent cause of a hereditary optic neuropathy with late manifestations (Moorman et al. 1993). The disease affects males 80–90% of the time but 18% of female carriers have some clinical manifestations. Seventy to 100% of daughters of female carriers are also carriers, while 50–100% of sons of female carriers are affected with transmission always through the female line. Several point mutations of mitochondrial DNA have been shown to be associated with the disease (Yen et al. 2006; Fraser et al. 2010; Koilkonda and Guy 2010; Yu-Wai-Man et al. 2011). Some of these mutations (den Hollander et al. 2006) probably act as primary mutations (‘major mutations’) while others may have only a contributory role (‘minor mutations’). The mechanism of the disease however, remains unknown. Onset is usually in adolescence or early adulthood (Riordan-Eva et al. 1995; Newman 2005) but the age of such may be quite variable, even in the same kinship.

LHON typically presents with blurred central vision in one eye. Similar symptoms usually occur in the opposite eye within a few days or weeks but the interval occasionally occurs in months or years. In about 20% of individuals the onset is simultaneous (Riordan-Eva et al. 1995) with colour vision affected and visual fields typically showing central or centrocecal defects. Fundoscopic examination at the initial stage shows a peculiar telangiectatic microangiopathy,
especially in the peripapillary region (Nikoskelainen et al. 1983) although this may be present in asymptomatic family members (Nikoskelainen et al. 1982). Fluorescein angiography-characteristically shows absence of peripapillary retinal staining (Nikoskelainen et al. 1984) while in symptomatic patients telangiectasias are accompanied by retinal oedema and haemorrhages. In later stages atrophy appears first in the maculopapillar bundle and then in the rest of the retina within 2 months of onset. At this stage a pale disc with narrow vessels is visible (Lopez and Smith 1986) with visual field loss progressing from an enlarged blind spot to a large centrocecal scotoma and loss of visual acuity usually severe to 6/60 or less. Although there is no specific treatment avoiding agents that might stress mitochondrial energy production may be a possible option in the future (Fraser et al. 2010; Koilkonda and Guy 2010; Yu-Wai-Man et al. 2011).

Hereditary optic atrophy with the characteristics of LHON has been reported in association with neurological symptoms and signs in some families. Associated neurological features have included ataxia and cerebellar manifestations that may suggest multiple sclerosis, dystonia and paraplegia which might result from a special susceptibility of patients with specific mitochondrial mutations associated with LHON like the 11778 mutation to demyelinating disease (Flanigan and Johns 1993; Hanefeld et al. 1994). Both the 11778 and the 3460 mutations in some women with multiple sclerosis with prominent and early optic nerve involvement (Kellar-Wood et al. 1994). Even classic forms may be associated with abnormalities of auditory evoked potentials (Mondelli et al. 1990), suggesting diffusion of lesions to the brainstem in two-thirds of affected individuals.

Individuals with optic atrophy and dystonia are of interest as they may also represent a mitochondrial disease (Novotny et al. 1986; Leuzzi et al. 1992). A ‘typical’ Leber optic atrophy with a mitochondrial myopathy has been described in a patient (Roger 1986) while the relationship between pure and complicated forms is being further clarified by DNA studies.

Several vitamin cocktails including coenzyme Q10 have been tried in LHON but the success has been limited. Avoiding stress in mitochondrial energy production may be beneficial, which leads to the suggestion of avoiding stresses such as tobacco and excessive alcohol (Kirkman et al. 2009).

There are several other forms of hereditary optic nerve atrophies. Autosomal dominant optic atrophy may occur very early in life, typically within the first or second decade in life which for most individuals has an insidious onset. The degree of vision loss is variable (Caldwell et al. 1971) and there may be limited vision loss in almost half the patients while examination shows disc pallor, especially in the temporal sector of the disc and central or centrocecal scotomata (Neetens and Martin 1996). There is no angiopathy at any stage of the disorder and this makes it easy to separate dominant optic atrophy and early LHON while the outlook of autosomal dominant optic atrophy is favourable as the condition is stationary in most individuals (Elliot et al. 1993).

Congenital dominant optic nerve atrophy is a rare variant of the more common type, with onset in the first decade of life. Symptoms typically present at 4–6 years at the time of vision screening with reduction in visual acuity variable and visual acuities of 20/200 or worse representing about 15% of individuals. Interestingly, there is significant intrafamilial variation. In addition to a visual acuity, reduction dyschromatopsia occurs along with typically central field deficits. Dominant optic nerve atrophy is believed to be a primary degeneration of the retinal ganglion cells. The long arm of chromosome 3 (3q28–q29) and chromosome 18q have been implicated (Kerrison et al. 1999; Delettre et al. 2002; Fraser et al. 2010; Yu-Wai-Man et al. 2011).

Autosomal recessive optic atrophy is rare and more severe than the dominant form (Moller 1992) and may occur in...
Compressive Optic Neuropathies

Compression on the optic nerve on one or both sides is a frequent feature of tumours of the diencephalons and less commonly, of the hypophysis. In a significant proportion of individuals optic neuropathy is the presenting manifestation and here it is important to make an early diagnosis and not accept a wrong diagnosis of demyelinating and vascular optic neuropathy.

Craniopharyngiomas and optic nerve gliomas are the most common causes of compression neuropathy but hypophysial tumours may rarely be the cause (Reid et al. 1985). The onset of visual symptoms may be acute and unilateral while classic features of bitemporal hemianopia as well as any neurological finding can be absent. Small children may present with nystagmus and as a result any child with new onset nystagmus should be investigated for the possibility of a chiasmatic tumour, even in the presence of a normal funduscopy examination. Growth retardation is often present and an important clue suggesting the possibility of diencephalic disease. Neuroimaging, especially MRI, is essential for a precise diagnosis and should be performed whenever there is doubt about the origin of the optic nerve disorder (Eidelberg et al. 1988).

Increased Intracranial Pressure and the Optic Nerve

Children with increased intracranial pressure may present with transient or permanent visual symptoms. Visual field loss is more common over visual acuity loss in children developing papilloedema with field deficits including enlarged blind spot, nasal field defects especially inferonasal, disk-related arcuate scotomata and global constriction. Other ophthalmic presentations are double vision and strabismus secondary to abducens palsy, retro-orbital pain and photophobia especially in prepubertal children. Following prompt diagnosis and treatment resolution of disk swelling and improvement of visual function is expected in patients with mild to moderate papilloedema.

All individuals suspected to be affected by increased intracranial pressure must undergo ophthalmological assessment. Dilated fundoscopy allows careful assessment of the optic nerve head and fundus photography can be used to monitor changes over time. Assessment of thickening of the peripapillary retinal nerve fibre layer by OCT is useful while early visual loss is best detected by visual field assessment. Visual fields can be used not only to diagnose but also to monitor progress and treatment with the goal of the latter to relieve symptoms and preserve vision.

Toxic and Nutritional Optic Neuropathies

A large number of chemicals, especially drugs, can be the cause of optic neuropathy (Sipos and James 1983). Isoniazide, ethambutol, streptomycin, chloramphenicol, penicillinamine, quinine, ergot derivatives and chloropropamide are among the most important incriminated agents. The halogenated hydroxyquinolines have been responsible, especially in Japan but also less commonly in occidental countries for an optic neuropathy associated with peripheral and spinal involvement (Behrens 1974). This subacute myelo-optic neuropathy has substantially regressed since the dangers of these drugs have been publicised. Prolonged use of Linezolid, used in the treatment of Gram-positive infections, is associated with reversible optic neuropathy (Rucker et al. 2006) while intra-arterial chemotherapy has been implicated as the origins of some optic atrophy.
following therapy for intracranial tumours (Kupersmith et al. 1988). Immunomodulatory agents such as infliximab has been associated with optic nerve toxicity following use in the treatment of Crohn’s disease, ulcerative colitis and psoriatic arthropathy (Chan and Castellanos 2010).

Nutritional deficiencies, in particular deficiencies in vitamin B12 and folic acid, can also be responsible for optic neuropathy leading to vision loss (Knox et al. 1982). In developed countries this is unusual but has been reported in the context of anorexia nervosa (Moschos et al. 2010). This may be relevant especially in some of the syndromes of optic atrophy, ataxia and neuropathy observed in tropical countries.

**Demyelinating Optic Neuropathies**

Unilateral and bilateral optic neuritis will be reviewed more fully in Chapters 11 and 12. Multiple sclerosis is less common in children. The relationship to optic neuritis is also much less than in adults, especially when optic involvement is bilateral, although this remains controversial (Parkin et al. 1984; Kriss et al. 1988; Riikonen et al. 1988). As with adults, T2 lesions on MRI are associated with an increase risk of developing MS (Cakmakli et al. 2009; Absoud et al. 2011). Optic neuritis following specific infectious diseases has been recorded following measles, rubella, varicella (Purvin et al. 1988b; Selbst et al. 1993), Epstein-Barr virus infection (Purvin et al. 1988a) and cowpox B5 infection (Spalton et al. 1989). Optic neuritis may occur in sinus disease (Awerbuch et al. 1989) and sarcoidosis (Graham et al. 1986; Chapelon et al. 1990).

Typically, children present with vision loss either acutely or over a few days and the loss of visual acuity and visual fields can be profound. In the presence of bilateral disease the pupils may be dilated even under brightly lit circumstances while clinically the optic discs are swollen. The standard treatment remains high-dose steroids.

**Vascular Optic Nerve/Retinal Disease**

The most common cause of vascular retinal disease is migraine (see also Chapter 17), which may be responsible for monocular loss of vision ipsilateral to the side of the headache. Vision loss constitutes the aura of a migraine and may be partial or total. Rarely, migraines may be characterised by monocular blindness without headache. Vision loss generally clears in a few minutes, but an occasional patient may be left with permanent vision loss. Although patients who develop persistent blindness often have other risk factors for vascular disease vision loss has been reported in some adolescents without such risk factors (Coppeto 1986). Patients with monocular attacks of blindness as a manifestation of migraine (retinal migraine) should be investigated and treated urgently to prevent permanent impairment with treatment of such patients similar to typical migraines, sometimes supplemented by anti-aggregant drugs like aspirin. Transient bilateral loss of vision is often related to migraine in young patients (Tippin et al. 1989) and same applies to post-traumatic transient blindness (Greenblatt 1973).

Central retinal artery obstruction may be the result of emboli to the retinal artery as a result of congenital heart disease (Brown et al. 1981). Other causes include coagulopathies, various types of vasculitis, mitral valve prolapse, cardiolsip antibody syndrome, and cardiac catheterisation (Jackson et al. 1984; Kosmorsky et al. 1988). The onset of symptoms is usually abrupt with a sudden unilateral loss of vision that may be partial or complete with altitudinal defects present in a majority of individuals. Ophthalmological examination shows swelling of the optic disc, oedema of the retina and narrowing of the arteries followed by thickening of the arterial wall while haemorrhages may be present. Fluorescein angiography can provide objective confirmation of the diagnosis and accurately shows the topography and degree of ischaemia (Chutorian et al. 2002). Treatment depends on the cause: anticoagulants may be indicated if the source of the emboli is identified while steroids and immunosuppressors are useful for many vasculitides. The outlook for vision depends on the cause of the obstruction and on the location of the obstructed vessels with the prognosis better for obliteration of the peripheral branches than for that of the central artery itself.

It is worth mentioning the ophthalmological finding of the cherry red spot seen in central artery occlusion which appears several hours after the occlusion. In this circumstance the spot is seen because the macula receives blood supply for the choroid below but the surrounding retina is pale as a result of the infarction.

**Coats disease** is characterised by congenital retinal tel-angiectasias, aneurysmal retinal vessel dilation and capillary microaneurysms with associated subretinal and intraretinal exudation. Many individuals are affected by Coats disease sporadically but a somatic mutation in the NDP gene has been described (Black et al. 1999). In addition, it can be part of a rare autosomal recessive syndrome of facioscapulohumeral dystrophy, hearing loss and intellectual disability (Taylor et al. 1982; Matsuzaka et al. 1986). Other syndromes including Cornelia de Lange Hallerman-Striiff, and Senior-loken have been associated with this condition (Newell 1994; Schuman 1995; Barakat et al. 2009). Bilateral Coats disease, facial dysmorphisms, abnormal hair and nails as well as striking supra- and infratentorial calcification involving the thalami and neighbouring brain areas have been reported as familial disorders (Tolmie et al. 1988; Goutieres et al. 1999) (Fig. 22.3).

**VISUAL IMPAIRMENT DUE TO RETINAL DISORDERS**

A wide variety of congenital retinal diseases exist, representing a heterogeneous group of children. Often such diseases may be classified as either static, progressive or alternatively according to whether the disease is predominantly rod or cone. For
the majority of conditions such as retinitis pigmentosa, achromatopsia and retinal dystrophies a paediatric ophthalmology text will provide greater detail.

Retinal disorders include genetic, traumatic, inflammatory deficiency and vascular diseases. Several infectious disorders can produce retinitis, especially the exanthematous diseases of childhood (Marshall et al. 1985). Early recognition of retinal conditions may be important in the management: for example, choroidoretinitis may be the first manifestation of subacute encephalitis and remains isolated for several months or even years. This disease should be included in the differential diagnosis of retinal disorders as early treatment is potentially useful (Tomoda et al. 1997).

Inherited Retinal Diseases

Leber's congenital amaurosis is an inheritable generalised rod and cone dystrophy that presents early in childhood which may be progressive in some individuals. Leber's congenital amaurosis presents as blindness or very limited vision with nystagmus from birth or the first months of life with children often demonstrating blindisms such as eye pressing. With time the fundus examination may show pallor of the optic discs, thinned retinal vessels, clumps of retinal pigment or white punctate retinopathy or be altogether normal (Schroeder et al. 1987). Extinction of the ERG is an essential diagnostic feature, typically inherited as an autosomal recessive condition (Lambert et al. 1993), while some affected children have hypotonia, seizures and intellectual disability. In the past it was responsible for a larger proportion of congenital blindness, however, this is no longer the case because of other conditions, primarily cortical visual impairment.

These dystrophies are known to occur in association with structural defects of the CNS such as encephalocoeles (Vaizey et al. 1977), microcephaly (Cantu et al. 1977) and anomalies of the cerebellar vermis (Dekaban 1975; Weinstein et al. 1984; Marchal et al. 1989; Funakawa et al. 1995). Hypoplasia of the vermis has been found in 10% of the cases (Nickel and Hoyt 1982) while retinal degeneration may also be associated with various renal defects (Proesmans et al. 1975; Godel et al. 1978; Rizzo et al. 1986; Warady et al. 1994) or be a part of complex syndromes (Mainzer et al. 1970; Rizzo et al. 1986).

A similar phenotype has been found in patients with peroxosomal disorders such as Zellweger syndrome as well as in individuals with few other abnormalities suggestive of a peroxosomal defect (Ek et al. 1986). Such heterogeneity probably accounts for the variable frequency with which neurodevelopmental signs are found in infants with congenital retinal degeneration, with figures as low as 3% (Noble and Carr 1978) or as high as 25–37% (Schaap-Kimmiger et al. 1959). A review of 75 individuals affected by Leber congenital amaurosis found 30 different conditions including Joubert syndrome, Zellweger syndrome, infantile Refsum disease, congenital stationary night blindness and achromatopsia (Lambert et al. 1989).

As noted above, many of the conditions associated with Leber congenital amaurosis are associated with intellectual disability however in ‘pure (single gene defect) form’ neurodevelopmental conditions are rather uncommon. It is transmitted as an autosomal recessive trait (Lambert et al. 1993) and a gene has been mapped to chromosome 17p (Camuzat et al. 1995). Most of the ‘non-pure’ conditions are probably transmitted as mendelian recessive traits (Alstrom and Olson 1957; Baker et al. 1995; Casteels et al. 1996; Taylor 1997). Structural CNS defects and neurological and cognitive dysfunction are more frequent (Vaizey et al. 1977).

These conditions are genetically heterogenous with multiple genes being identified (den Hollander et al. 2006, 2008). Molecular testing can now identify the gene in over 50% of individuals. With the advent of better diagnostic measures therapeutic interventions are now being considered through gene therapies. Although there appears to be reasonable safety profile the results are variable (Bainbridge et al. 2008).

In the presence of a retinal dystrophy, the cherry-red spot is a worrisome finding. It is observed in several gangliosidoses and lipidoses storage disorders such as Tay-Sachs disease and Niemann Pick type A (see Chapter 9) with the appearance due to a relative transparency of the macula. Typically, storage disorders accumulate material within the cell layers of the retina: as the macular is just a thin layer there is less accumulation in this area which allows the redness of the choroid to be observed.
Other Hereditary Pigmentary Retinopathies (Retinitis Pigmentosa)

A number of other progressive pigmentary degenerations of the retina can be the cause of progressive visual loss in association with neurological dysfunction (see Fig. 22.4). The major initial symptom is nyctalopia followed after a variable time by concentric narrowing of the visual field and decrease in visual acuity with the disease onset variable. The ERG is abnormal early but fundus examination may remain normal for long periods. If patients present with nystagmus they are more likely to have rod-cone/cone-rod diseases. There are two main groups of pigmentary retinopathy: in one, only the eyes are involved while in the second retinal disease is associated with neurodegenerative disorders. These include individuals affected by Leigh syndrome, the ceriod-lipofuscinoses, abetalipoproteinemia, the mucopolysaccharidoses, several types of cerebellar or spinocerebellar degenerations and genetic syndromes such as the Laurence-Moon, Alstrom-Hallgren and Usher syndromes. Among the isolated pigmentary retinopathies multiple types exist with variable inheritance (X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). While there is genetic heterogeneity within each inheritable class: X-linked, autosomal recessive and dominant). 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commonly strabismus (Gibson et al. 1990). These children commonly have neurological and developmental disabilities. ROP is classified based on the four criteria: severity (stages 1–5), location (zones 1–3), extent of retinal involvement (hours) and plus disease (clinical description of activity) (Committee for the Classification of Retinopathy of Prematurity 1984; International Committee for the Classification of the Late Stages of Retinopathy of Prematurity 1987).

The majority of children with ROP undergo complete resolution, typically those with low stages however those with higher stages may have a reduction in visual acuity (Holmstrom et al. 1999). Many children will have some reduction in visual fields (Cryotherapy for Retinopathy of Prematurity Cooperative Group 2001) but the clinical consequence may not be that evident. Many children will have additional ocular consequences including refractive errors and strabismus (Holmstrom et al. 1999).

The mainstay of therapy has been with the use of laser and cryotherapy performed by the ophthalmologist. Anti-VEGF therapies are now being used which minimises the angiogenesis associated with ROP (Mintz-Hittner et al. 2011).

Other Retinal Disorders

There are many retinal conditions that may lead to a loss in visual acuity many of which are associated with neurological disorders. These conditions range from infectious diseases, especially toxoplasmosis (Fig. 22.6) and cytomegalovirus infections, to congenital anomalies such as the retinal ‘lacunae’ of Aicardi syndrome (Fig. 22.7). Fundoscopic abnormalities may also be seen in several metabolic diseases.

Vitamin E deficiency has associated retinal involvement with peripheral neuropathy and oculomotor dysfunction often accompanying this condition. Vitamin A deficiency is a common reason for vision loss in developing countries: a deficiency of such, rare in Western countries, is usually caused by a combination of malnutrition and malabsorption due to intestinal infections. Clinically there is slow dark adaptation: peripheral fields may be affected as rod dysfunction occurs, while improvement can occur with vitamin A supplementation.

Vigabatrin is becoming an important cause of retinal toxicity. In paediatrics, it is a first line treatment for infantile spasms and can be used for other forms of refractory seizures. Infants affected by peripheral field loss associated with vigabatrin were first described in 1997 (Eke et al. 1997) and since then vigabatrin has been correlated to cause concentric peripheral visual field loss thought to be the result of the cumulative retinal dose of the drug (Malmgren et al. 2001). Active surveillance with ophthalmological assessment and visual field testing when possible has been suggested. Other tests such as OCT, VEP, and ERG may be unreliable in assisting in the diagnosis.

Vitreoretinal Diseases

There are a number of diseases that result from abnormalities of the vitreous. Vitreoretinal dysplasias result from the maldevelopment of the vitreous and retina. Abnormalities of the vitreous may lead to several congenital anomalies such as persistent hyaloid artery, while in the majority of individuals the hyaloid artery regresses and, therefore, visual impairment does not occur. A less common condition is persistent hyperplastic primary vitreous, caused by the failure of the primary vitreous...
Chapter 22 Disorders of Visual and Oculomotor Functions

Vitreoretinal dysplasias can occur in isolation or associated with other comorbid conditions that can involve one or both eyes. Common conditions include Norrie disease, familial vitreoretinopathies, juvenile retinoschisis, trisomy 13 and incontinentia pigmentosa.

Norrie disease is a sex-linked recessive disorder characterised by bilateral retinal folds, retinal detachment, vitreous haemorrhage and bilateral retrolental masses that may be a cause of congenital or early onset blindness in boys. Phenotypes are variable. About 25% of affected males also develop cochlear hearing loss (Liberfarb et al. 1985) and developmental disability is also common. A more severe phenotype has been found in children with large chromosomal deletions (Suarez-Merino et al. 2001) and mutations of the responsible gene can be used in genetic diagnosis (Black and Redmond 1994). Cataplectic episodes may be associated with this condition.

Familial exudative vitreoretinopathy are another group of inherited forms of visual impairment. They are characterised by abnormal retinal vascularisation, exudation, neovascularisation and tractional retinal detachments. There are several modes of inheritance, with the X-linked form leading to severe early onset visual impairment. A variety of molecular genetic studies have been performed, showing the complex nature of the phenotypic presentation (Qin et al. 2005).

Juvenile X-linked retinoschisis is an X-linked disorder characterised by the cystic spoke-wheel-like maculopathy, with children typically presenting with a reduction in visual acuity or strabismus. Whereas in trisomy 13 the fundoscopic examination identifies disorganisation of the vitreous and retina often other ocular abnormalities are seen including microphthalmos, corneal opacities, cataract and dysplasia of the optic nerve.

Structural Causes of Visual Impairment

There are many structural abnormalities of the eye with the vast majority not primarily presenting to the neurologist, one of the most common conditions being cataracts. Congenital cataracts or lens opacities are a frequent cause of visual defects in children and if identified early can be removed and vision preserved. However, the clinician should be aware of the great association with additional neurological conditions such as the mucopolysaccharidoses, galactosaemia, intrauterine infections, chromosomal aberrations and other syndromes (Kohn 1976). The visual outcomes for the majority are excellent with early treatment but poorer outcomes are associated with delays in diagnosis and/or associated ocular or systemic conditions that may independently lead to visual impairment.

A number of other ocular structural conditions such as anophthalmos, nanophthalmos and microphthalmia are rare. Along with coloboma the group is associated with a variety of chromosomal anomalies, genetic diseases and systematic conditions including the brain, cardiac and renal systems.

Aniridia may present to the neurologist as an abnormality in pupillary response. Aniridia is a structural eye defect. Typically, infants present with nystagmus, hypoplasia of the iris, unresponsive pupils and light sensitivity. Mutations in the PAX6 gene are commonly responsible (Prosser and van Heyningen 1998). Patients may present with a family history of the condition, presenting as an autosomal dominant form: for sporadic patients evaluation for Wilms tumour is required, as the PAX6 gene is located near the WT1 gene (Gronskov et al. 2001). This condition may be also associated with genitourinary abnormalities and intellectual disability, the so called WAGR association. The condition has variable reductions in

Figure 22.7 Aicardi syndrome. (a) Typical ‘lacunae’ in left fundus oculi at age 9 months and (b) at age 4½ years. The size of the ‘lacunae’ has not changed but the amount of pigment has increased. The peripapillary location of the lesions is usual. (Courtesy Dr I McCormick, Children’s Hospital, Vancouver.)
visual acuity and as a result not all patients will have a visual impairment.

**NYSTAGMUS**

Nystagmus (Table 22.5) is typically an involuntary, rhythmic, conjugate oscillatory movement of the eyes (Dell’Osso 1984; Hoyt 1987; Troost 1989) that may occur in any plane and is one of the most common characteristics of children with visual impairment, with the estimated prevalence is 24 in 10,000 (Sarvananthan et al. 2009). It is due to dysfunction of the complex mechanisms that maintain ocular fixation with the clinical description of nystagmus usually based on the direction of the fast component and is termed horizontal, vertical or rotary or any combination of these. The nystagmus may be conjugate or dysconjugate. A long recognized distinction is between jerk nystagmus, in which there is a slow initiating component followed by a fast corrective component and pendular nystagmus in which the oscillations are of equal speed. However the distinction between jerk and pendular oscillations may be difficult and even meaningless as the form of eye movements may change with gaze or other factors. In pendular nystagmus the oscillations are slow in each direction, at least in the primary position of gaze, but may change to jerk nystagmus on lateral gaze. The most common form of jerk nystagmus is gaze evoked nystagmus due to a deficit in the mechanisms responsible for holding the eyes in an eccentric position whose seat is in the posterior fossa. The intensity of jerk nystagmus increases in the horizontal plane when gaze is in the direction of the fast phase (Alexander’s law).

Nystagmus should be differentiated from roving eye movements of blind children with pregeniculate lesions. Such movements are indicative of extremely poor vision or complete blindness and may be replaced by nystagmus when some useful vision develops in infants a few months of age (Jan et al. 1986; Kompf and Piper 1987).

**ACQUIRED NYSTAGMUS**

Acquired nystagmus is usually of the jerk type with a horizontal or horizontal-rotary form with the main causes indicated in Table 22.6. It is important to keep in mind that drug toxicity is a common cause of jerk nystagmus of horizontal or vertical types and certain forms of nystagmus such as seesaw and downbeat nystagmus (Hanegan et al. 1983) are electively caused by certain conditions like chiasmal lesions of a Chiari I malformation.

Nystagmus can be the result of many neurological diseases. New onset acquired nystagmus may present with vertigo, nausea, dizziness and oscillopsia. The type of nystagmus may point to certain aetiological causes meaning that neuroimaging is required to rule out central causes such as demyelinating
Table 22.6 Various types of acquired nystagmus

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
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<tbody>
<tr>
<td><strong>Seesaw nystagmus</strong></td>
<td>Rostral midbrain lesions</td>
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<td></td>
<td>Parasellar lesions (e.g. pituitary tumours)</td>
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<td></td>
<td>Visual loss secondary to retinitis pigmentosa</td>
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<tr>
<td><strong>Downbeat nystagmus</strong></td>
<td>Lesions of the vestibulocerebellum and underlying medulla (e.g. Arnold-Chiari malformation, microvascular disease with vertebrobasilar insufficiency, multiple sclerosis, Wernicke's encephalopathy, encephalitis, lithium intoxication)</td>
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<td>Heat stroke</td>
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<td></td>
<td>Approximately 50% have no identifiable cause</td>
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<tr>
<td><strong>Upbeat nystagmus</strong></td>
<td>Medullary lesions including perihypoglossal nuclei, the adjacent medial vestibular nucleus and nucleus intercalatus (structures important in gaze holding)</td>
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<td>Lesions of the anterior vermis of the cerebellum</td>
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<td></td>
<td>Benign paroxysmal positional vertigo</td>
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<tr>
<td><strong>Periodic alternating nystagmus</strong></td>
<td>Arnold-Chiari malformation</td>
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<td>Demyelinating disease</td>
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<td></td>
<td>Spinocerebellar degeneration</td>
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<td>Lesions of the vestibular nuclei</td>
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<td>Head trauma</td>
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<td>Encephalitis</td>
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<td>Syphilis</td>
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<td>Posterior fossa tumors</td>
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<td>Binocular visual deprivation (e.g. ocular media opacities)</td>
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<tr>
<td><strong>Pendular nystagmus</strong></td>
<td>Demyelinating disease</td>
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<td>Monocular or binocular visual deprivation</td>
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<td></td>
<td>Oculopatellar myoclonus</td>
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<td>Internuclear ophthalmoplegia</td>
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<td></td>
<td>Brainstem or cerebellar dysfunction</td>
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<tr>
<td><strong>Spasmus nutans</strong></td>
<td>Usually occurs in otherwise healthy children; may be caused by chiasmal, suprachiasmal, or third ventricle gliomas</td>
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<tr>
<td><strong>Torsional</strong></td>
<td>Lateral medullary syndrome (Wallenberg’s syndrome)</td>
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<tr>
<td><strong>Abducting nystagmus of internuclear ophthalmoplegia</strong></td>
<td>Demyelinating disease</td>
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<tr>
<td></td>
<td>Brain stem stroke</td>
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<tr>
<td><strong>Gaze-evoked</strong></td>
<td>Drugs: anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) at therapeutic dosages</td>
</tr>
</tbody>
</table>

CONGENITAL/INFANTILE NYSTAGMUS

Congenital nystagmus is usually recognised shortly after birth but it may be later in the latent type which may not be detected until the visual acuity testing. It may be delayed up to several months of age especially when sensory in type, persisting throughout life. There is no widely accepted classification of nystagmus and often congenital nystagmus may be categorised into congenital idiopathic nystagmus, sensory defect nystagmus and neurological nystagmus.

There are numerous causes of congenital nystagmus. It may be genetically determined and can be transmitted as an autosomal recessive, autosomal dominant or X-linked condition (Dell’Ossi et al. 1974). In addition many genetic syndromes such as Down syndrome and Noonan syndrome are associated with nystagmus.

Congenital nystagmus usually oscillates in a constant direction with up to 40 wave forms having been described, most of which are specific for congenital nystagmus. Often the assessment of wave forms requires specialised equipment but such recordings are difficult to calibrate in children (Baker et al. 1995), meaning that clinical examination is essential.

Clinically, congenital nystagmus remains horizontal during vertical gaze rather than converting to gaze-evoked vertical nystagmus (Troost 1989). Head nodding or shaking is present in 6.6–8.0% of children with congenital nystagmus, regardless of the type (idiopathic or sensory) and the mode of inheritance (Jan et al. 1990). It may be a means to improve foveation time and therefore visual acuity. A reduction in visual acuity is seen in about half the children (Dell’Osso et al. 1974; Troost 1989; Jan et al. 1990), but in the presence of ‘sensory’ nystagmus lower visual acuity is common (Jan et al. 1990).
Congenital nystagmus is usually associated with strabismus and other ocular abnormalities (Hertle and Dell’Osso 1999; Abadi and Bjerre 2002). Additional features of congenital nystagmus are described in Table 22.7. A unique feature of congenital nystagmus is the so-called inverted optokinetic nystagmus where the fast components are in the direction of rotation of the drum instead of the opposite, which is normal (Halmagyi et al. 1980).

In patients with albinism nystagmus is commonly seen and often jerk nystagmus may reverse direction. Interestingly, children with albinism have an excess proportion of undescussed retinofugal fibres so that the innermost parts of the nasal fields have a crossed cortical projection. This anomaly can be detected by study of the visual evoked potentials and in some patients by MRI demonstrating a sagittally split chiasma (Apkarian et al. 1995).

Common causes of jerk nystagmus includes vestibular and gaze evoked nystagmus. Vestibular nystagmus is also a common type of jerk nystagmus and may result from involvement of the vestibular end organ or central pathways and nuclei (Daroff et al. 1978). Central causes are usually uniplanar in contrast to peripheral causes which are commonly torsional or multiplanar. Visual fixation typically inhibits peripheral vestibular nystagmus but not central vestibular nystagmus. While in gaze-evoked nystagmus the jerk nystagmus occurs in the direction of eccentric gaze. Posterior fossa structural diseases are commonly implicated. Drugs, particularly anticonvulsants, are also known to lead to the phenomenon.

Patients with Pelizaeus-Merzbacher disease can present with an unique kind of nystagmus that is not seen in other neurodegenerative disease which is a combination of elliptical pendular and upbeat nystagmus (Trobe et al. 1991). If observed in the context of supportive clinical history and imaging a presumptive diagnosis can often be made.

In periodic alternating nystagmus the null point shifts position in a cyclic pattern. Periodic alternating nystagmus is typically congenital and benign but has been associated with neurodegenerative conditions such as ataxia-telangiectasia, and vestibulocerebellar lesions (Shallo-Hoffman and Riordan-Eva 2001). In some patients periodic alternating nystagmus may respond to oral baclofen while other less common types of nystagmus are summarised in Table 22.7.

Latent nystagmus occurs when a single eye is covered. It may be ‘manifest latent’ in children with strabismus who are actually viewing with a single eye at a time even though both eyes are open.

### Table 22.7 Main features of congenital nystagmus

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binocular</td>
</tr>
<tr>
<td>Similar amplitude in both eyes</td>
</tr>
<tr>
<td>Uniplanar, usually horizontal (may be vertical, rotary)</td>
</tr>
<tr>
<td>Increased by attempts at fixation</td>
</tr>
<tr>
<td>Inversion of the optokinetic reflex</td>
</tr>
<tr>
<td>Associated head oscillations (in some types)</td>
</tr>
<tr>
<td>Abolished in sleep</td>
</tr>
<tr>
<td>Distinctive waveforms (require special recording systems)</td>
</tr>
</tbody>
</table>

Adapted from Troost (1989).

Although square wave jerks can be seen in normal patients they have been associated with cerebellar disease, progressive supranuclear palsy and multiple sclerosis (Dell’Osso et al. 1975).

Monocular vertical oscillations may also occur in amblyopic patients, know as the Heimann-Bielchowsky phenomenon (Smith et al. 1982). Many other types of ocular oscillations are also recognised.

Opsoclonus is characterised by chaotic, rapid oscillations in all planes of gaze. Opsoclonus is exceptionally observed in newborn infants (Hoyt 1977) and may also be seen in some viral infections as well as in association with neuroblastoma. In children with neural crest tumours or brainstem encephalitis opsinclusus is accompanied by diffuse or focal myoclonus. Ocular flutter and ocular hypermetria may be seen in patients with inflammatory or other disorders of the cerebellum (Cogan 1954).

Ocular motor apraxia (saccade initiation failure) is characterised by abnormal movements of the head and eyes when changes in gaze are being attempted. In complete form initiation of a saccade may take up to one second and the movement is slow and hypometric so that several successive hypometric saccades may be necessary to bring the eyes to the desired position. In fact, refixation is commonly performed by head turning rather than by eye deviation: during head rotation, there may be deviation of the eyes in the opposite direction (contraversion), with secondary realignment of the eyes and head when the new target has been reached (Zee et al. 1977). The anomaly is limited to horizontal saccades while vestibular reflex movements, pursuit (slow) movements and vertical saccades are normal.

For most patients ocular motor apraxia is idiopathic however for some it has been associated with chromosomal abnormalities (Martin Carballo et al. 1993) or with immune deficiency (Narbona et al. 1980). CNS anomalies such as delayed myelination, agenesis of the corpus callosum and cerebellar vermian abnormalities have been reported (Shawkat et al. 1995) which suggests lesional causes of delayed saccades may be more common. A small number of patients with vertical oculomotor apraxia have been described (Ebner et al. 1990; Hughes et al. 1985) with one shown to have had a bilateral lesion at the mesencephalic-diencephalic junction.

Ocular motor apraxia should be distinguished from abnormal eye movements observed in children with very poor visual
acuities who tend to use head movements rather than saccades for looking at targets (Jan et al. 1986) and in children with severe strabismus and low acuity. Syndromes of ocular motor apraxia with retinal dystrophy are known, with the most common being Joubert’s syndrome. These children have cerebellar vermian anomalies and often develop retinal dystrophies; the syndrome is also associated with renal cystic disease which ultimately leads to renal failure.

Ocular motor apraxia is observed as a specific congenital disease known as Cogan disease and in various CNS disorders including perinatal conditions like cerebral palsy, congenital malformations, neurodegenerative conditions, infections and tumours (Le Ber et al. 2003, 2004). Cogan disease is generally recognised after 6–12 months of age because of the occurrence of head thrusts that may be mistaken for tics or even epileptic seizures. Vertical saccades are normal and cognitive development is usually preserved, however, many children have motor difficulties and challenges with school performance (Rappaport et al. 1987; Marr et al. 2005). The disease is genetically determined in small numbers of patients, probably transmitted as a recessive trait with variability in clinical presentation, with some only having abnormalities with optokinetic nystagmus. The prognosis is generally favourable with a tendency towards improvement or better adaptation (Zee et al. 1977). In addition, older patients tend to use more unobtrusive manoeuvres than head thrusts such as forced blinking which breaks fixation which will allow refixation to occur.

Abnormal eye movements reminiscent of those with Cogan disease may be seen in association with callosal agenesis or vermian aplasia (Bordarier and Aicardi 1990; Leao and Ribeiro-Silva 1995; Kondo et al. 2007). Slowness of saccades has also been reported in Friedreich disease (Kirkham et al. 1979) and other rare spinocerebellar degenerations (Wadia and Swami 1971) including a syndrome of ataxia-ocular motor apraxia (Aicardi et al. 1988). Abnormal eye movements are also observed in children with albinism (Collewijn et al. 1985).

### PUPILLARY CONDITIONS

Although pupillary conditions do not lead to visual impairment they are important in the understanding of many serious neurological conditions such as Horner syndrome.
HORNER SYNDROME
(CLAUDE BERNARD-HORNER SYNDROME)

Horner syndrome comprises of three features (Weinstein et al. 1980): miosis, ptosis and anhidrosis of the face. For patients affected congenitally there is also heterochromia of the irides with deficient pigmentation on the affected side while in some individuals flushing of the face is present (Saito 1990). Instillation of norepinephrine produces little or no dilation. Horner syndrome is caused by sympathetic denervation, which may be congenital or acquired. It may be due to damage to the brachial plexus, especially the lower roots at birth or to tumours or other injuries that involve the superior cervical ganglion or the sympathetic trunks around the carotid artery. For a small number of individuals the syndrome is transmitted as a dominant trait (Hageman et al. 1992) and can be caused by lesions anywhere from the hypothalamus to the eye.

Horner syndrome should be distinguished from physiological anisocoria that may happen to be associated with mild ptosis of whatever cause, the so-called pseudo-Horner syndrome (Thompson et al. 1982), with the distinction important as Horner syndrome may have serious implications. Raeder syndrome differs from Horner syndromes by absence of facial anhidrosis and evidence of trigeminal involvement and often of other cranial nerves (Mokri 1982) with this syndrome indicating pathology in the region of the cavum of Meckel. For other patients experiencing the syndrome without involvement of other cranial nerves this may be a variant of migraine (Shevell et al. 1993).

ARGYLL ROBERTSON PUPIL AND OTHER RARE PUPILLARY ANOMALIES

Argyll Robertson pupil is classically associated with tertiary syphilis and, therefore, rarely observed in children, however the dissociation of light and near response may occur in other conditions such as pinealomas and other midbrain damage such as encephalitis, diabetes mellitus and some degenerative conditions.

Inverse Argyll Robertson pupil, that is pupils reacting to light but not convergence-accommodation, is rare and difficult to diagnose, as one should be certain that there is indeed an attempt at convergence.

The tonic pupil of Adie is rare in children. Typically it is idiopathic but has been associated with viral infections, ophthalmoplegic migraine and vaccinations (Goldsmith 1968; Aydin et al. 2006; Iannetti et al. 2009). It may be associated with hyporeflexia or areflexia and is thought to result from lesions in the ciliary ganglion with aberrant fibre regeneration. Hemifacial flushing and loss of sweating on exertion may be associated with the tonic pupil, absence of deep tendon reflexes and more widespread sympathetic dysfunction (Ross syndrome) or occur in persons with normal pupils, absence of deep tendon reflexes and more widespread sympathetic dysfunction (Ross syndrome) or individuals with normal pupils, the ‘harlequin syndrome’ (Drummond and Lance 1993). Bilateral congenital mydriasis has been observed in association with malformation of the posterior fossa with vermian agenesis (Richardson and Schulenberg 1992).

DISORDERS OF OCULAR MOTOR FUNCTION

INVolvement of peripheral ocular motor nerves or their nuclei

The movement of the eyeballs are controlled by the IIIrd, IVth and IVth cranial nerves through the muscles that they innervate. Paralysis of one or several of these muscles results in ophthalmoplegia which may be acquired or congenital and occur isolated or in combination. Such paralysis should be distinguished from nonparalytic strabismus which is a very common condition affecting 3–4% of all children. (For additional information, please refer to Leigh and Zee 2006.)

ACQUIRED OPHTHALMOPLEGIA

Ophthalmoplegia can be due to a large number of causes. Children with acquired ophthalmoplegia may present with double vision, head tilt and strabismus.

Acquired IIIrd nerve palsies are common. The most frequent causes (Table 22.9) are closed head trauma, infections, tumours and vascular causes including migraines (Ing et al. 1992). Typically the IIIrd nerve is damaged through the course taken as nuclear and fasciculat IIIrd nerve palsies are rare. If a nuclear IIIrd nerve palsy is present bilateral signs are likely to be present, whereas fascicular palsies tend to be unilateral. The age at onset and underlying cause are determining factors in the prognosis of the disease.

The most common cause of acquired IIIrd nerve palsy is trauma, with traumatic palsies resulting from haemorrhage or oedema into the nerves or muscles or from avulsion or lacerations of these structures (Miller 1985). The diagnosis of traumatic palsy may be difficult, particularly when the trauma has been minimal or not reported or when the paralysis is delayed or there are complications such as secondary orbital oedema, secondary increased intracranial pressure, infections or vascular disorders such as carotid-cavernous fistulae (Marmor et al. 1982). For such individuals neuroimaging investigation is indicated because trauma may be the only precipitating factor or paralysis of a nerve already compromised by a chronic (compressive) lesion.

Infection is the next most common cause, especially meningitis (Miller 1985), encephalitis and abscesses. Partial palsy
may be due to frontal sinusitis (Coker and Ros 1996) while tumours may present as an isolated IIIrd nerve palsy, especially craniopharyngiomas. With brainstem tumours other neurological signs become rapidly obvious: acute painful unilateral IIIrd nerve palsy may represent an ophthalmoplegic migraine, with there typically being a history of migraine. Generally, symptoms start in the first decade and resolve over a period of weeks with steroids possibly reducing the length of symptoms. Relapses can occur, however.

Acquired IVth Nerve Palsies

Acquired IVth nerve palsies are mainly of traumatic origin (Keane 1993). Avulsion of the superior oblique pulley may explain the relative frequency of the paralysis of this muscle (von Noorden et al. 1986), with the nerve open to injury by inflammation or compression in the long course (Sydnor et al. 1982) taken. Rare causes such as infection, tumours and raised intracranial pressure have also been documented. Nuclear and fascicular IVth nerve palsies typically result from posterior fossa tumours while fourth nerve paralysis is typically unilateral in more than 60% of patients and resolves in two thirds (Sydnor et al. 1982). The signs of acquired IVth nerve palsy are similar to individuals affected congenitally. Symptoms are diplopia with a combined vertical/horizontal separation plus (subjective incyclo) torsion maximal in downgaze, particularly symptomatic in bilateral cases: clinically this may present with difficulties in descending stairs. IVth nerve palsies often clear spontaneously after several months but infrequently they persist or show evidence of aberrant regeneration, the first signs of which may appear by 4–6 weeks following the causal lesion or infection (Walsh and Hoyt 1969; Miller 1985).

Table 22.9 Causes and clinical features of acquired ocular motor nerve paralysis

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Clinical features</th>
<th>Main causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor nuclei</td>
<td>Bilateral involvement frequent, often associated with gaze palsies. Internal ophthalmoplegia indicates midline lesion. Symmetrical ptosis may exist in isolation</td>
<td>Brainstem tumours and other tumours (pineal region, diencephalon). Infections and inflammation, e.g. brainstem encephalitis, multiple sclerosis. Vascular disease and vascular malformations. Degenerative diseases (Wernicke, Leigh)</td>
</tr>
<tr>
<td>Fascicular portion (between nuclei and emergence from peduncle)</td>
<td>Similar to nuclear involvement but rarely bilateral</td>
<td>Brainstem intrinsic disease</td>
</tr>
<tr>
<td>Interpeduncular fossa</td>
<td>May be associated with involvement of pyramidal tract. Pupillary dilatation and accomodative paralysis present</td>
<td>Basilar meningitis. Aneurysms of rostral basilar artery (rare). Dermoid cysts</td>
</tr>
<tr>
<td>At or near entrance into dura</td>
<td>Pupillary involvement prominent especially with herniation</td>
<td>Frontal trauma. Aneurysms. Transtentorial herniation from expanding supratentorial masses or haematomas</td>
</tr>
<tr>
<td>In cavernous sinus</td>
<td>Associated involvement of other nerves (V, VI, IV, oculosympathetic)</td>
<td>Sinus thrombosis. Aneurysms. Carotid–cavernous fistulas. Pituitary adenomas. Chordomas and other basilar tumours</td>
</tr>
<tr>
<td>Orbital apex and/or superior orbital fissure</td>
<td>Involvement may be partial as the nerve divides into two branches. Pupillary involvement only with affectation of lower trunk</td>
<td>Tolosa–Hunt syndrome. Orbital pseudotumour. Orbital cellulitis. Orbital tumours</td>
</tr>
<tr>
<td>Diffuse, undetermined or variable</td>
<td>Variable. Associated paralyses in some cases</td>
<td>Ophthalmoplegic migraine. Sarcoidosis, Whipple disease, some toxic causes such as drugs (e.g. anticonvulsants, aspirin). Miller Fisher syndrome and related cranial polyneuropathies, postviral palsies. Diabetes mellitus (exceptional)</td>
</tr>
</tbody>
</table>

Acquired VIth Nerve Palsies

As with the other oculomotor cranial nerves the most common cause of VIth nerve palsy in infants is trauma but other pathologies including tumour, infection and increased intracranial pressure may also lead to paresis (Table 22.10). Paralysis of the VIth nerve is sometimes observed in newborn infants, probably as a result of birth trauma (de Grauw et al. 1983), and usually disappears spontaneously in a few weeks. Tumours are the most common cause in older children and the nerve is especially sensitive to any cause of high intracranial pressure including pseudotumour cerebri. Meningitis and postnatal trauma can also produce lateral rectus paralysis (Afifi and Menzes 1992). Acquired paralysis of the VIth nerve may be difficult to distinguish from the sudden appearance of a squint due to a decompensation of refractive error or other visual disturbance, often at the time of an acute infectious disorder (Watson and Fielder 1987).
Postinfectious VIth nerve palsy secondary to a viral infection may be diagnosed on the basis of history although the diagnosis is often made without definitive proof. The onset is sudden and the involvement is generally unilateral with the child complaining of diplopia and the paralytic strabismus is observed. Full motility is restored within 6–12 months although a recurrent form has been reported (Afifi et al. 1990; Cohen et al. 1993).

Involvement of the VIth nerve may be a part of the Gradenigo syndrome which commonly occurred as a complication of mastoiditis when the infection reached the apex of the petrous, though individuals suffering from such are now exceptional. The proximity of the cavum trigeminale causes the Vth nerve to also be affected with pain in the face and eye and the facial nerve may be involved in the petrous canal. Gradenigo syndrome can be a consequence of T-cell lymphoma (Norwood and Haller 1990) on rare occasions. The syndrome is now more commonly seen with orbital or retro-orbital disease (Taylor 1997).

**Combined Ophthalmoplegias**

On occasion, ophthalmoplegia may involve a combination of nerves, an example of which is the Miller Fisher syndrome. Miller Fisher syndrome, a variant of Guillain-Barre syndrome, results in ophthalmoparesis of one or a combination of the IIIrd, IVth and VIth cranial nerves with pupil involvement and is associated with the presence of serum anti-GQ1b IgG antibodies. The involvement appears to be primarily in the periphery, although some oculocephalic manoeuvres may suggest a supranuclear component. Typically function slowly recovers spontaneously or following treatment with plasmapheresis with an association observed following Campylobacter jejuni infection, which is thought to induce antiganglioside antibodies (Ang 2001).

Another example of a combined ophthalmoplegia is the Tolosa-Hunt Syndrome (Fig. 22.8). Tolosa-Hunt syndrome is characterised by a dull, persistent pain around the affected eye, ophthalmoplegia and sometimes involvement of the optic nerve, the first and/or second branches of trigeminal nerves and sympathetic innervation of the affected eye (Goto et al. 1989; Gordon 1994). The IIIrd nerve is usually involved first and more severely than the others but all three oculomotor nerves may be affected. The diagnosis requires exclusion of the other known causes of painful ophthalmoplegia such as infection, neoplasm or lymphoma (Spector and Fiandaca 1986). CT may show a high-density area in the orbit and orbital phlebography may show occlusion of the superior ophthalmic vein (Goadsby and Lance 1989). While detailed imaging of the cavernous sinus is now essential in the investigation of apparently isolated and even painless, cranial nerve palsy. The course usually extends over weeks or rarely months, with

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**Table 22.10 Causes and clinical features of paralysis of the abducens and trochlear nerve**

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Clinical features</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus of IVth nerve</td>
<td>Difficult to determine and to differentiate from IIIrd nerve nuclei involvement and from supranuclear lesions</td>
<td>Brainstem tumours. Inflammatory or demyelinating disease. Vascular obstruction and malformations</td>
</tr>
<tr>
<td>Peripheral IVth nerve</td>
<td>Difficult to make a topical diagnosis. Head tilt toward the opposite shoulder</td>
<td>Head trauma</td>
</tr>
<tr>
<td>Nucleus of VIth nerve</td>
<td>Conjugate gaze palsy to the ipsilateral side. Does not produce isolated lateral rectus palsy</td>
<td>Same as IVth nerve nucleus involvement</td>
</tr>
<tr>
<td>Subarachnoid segment of VIth nerve</td>
<td>Isolated lateral rectus palsy</td>
<td>Aneurysm of basilar artery or its branches. Space-occupying supratentorial lesion (downward movement of neuraxis). Arnold–Chiari malformation. Meningitis and infiltration of the basal meninges</td>
</tr>
<tr>
<td>Extradural VIth nerve</td>
<td>Gradenigo syndrome. Involvement of VIth nerve and gasserian ganglion: pain in the face, reduced corneal sensitivity</td>
<td>Mastoiditis. Rarely bone tumours</td>
</tr>
<tr>
<td>Inferior petrosal sinus</td>
<td>May be similar to Gradenigo syndrome</td>
<td>Mastoiditis. Dural arteriovenous malformations of posterior fossa. Fracture of temporal bone. Primitive trigeminal artery</td>
</tr>
<tr>
<td>Cavernous sinus and/or superior orbital fissure</td>
<td>Associated involvement of other cranial nerves</td>
<td>Aneurysm, carotid cavernous fistulae, tumours, thrombosis of cavernous sinus</td>
</tr>
<tr>
<td>Sphenopalatine fossa</td>
<td>Loss of tearing due to involvement of 2nd division of VIth nerve</td>
<td>Tumours of skull base</td>
</tr>
<tr>
<td>Orbit</td>
<td>Indistinguishable from myogenic involvement except by electromyography</td>
<td>Tumours, inflammatory lesions</td>
</tr>
<tr>
<td>Diffuse, undetermined or variable</td>
<td>Isolated VIth nerve palsy</td>
<td>Postinfectious paralysis, diabetes (rare), migraine (rare), cranial polyneuropathy and Miller Fisher syndrome</td>
</tr>
</tbody>
</table>
corticosteroid administration valuable in the treatment and frequently having a dramatic effect. The condition is related to orbital pseudotumour (Rohr and Gauthier 1988; Grossniklaus et al. 1995), which may be either acute or chronic, with this so-called sclerosing orbital pseudotumour (Abramovitz et al. 1983) not responding to steroids. Pseudotumour is rarely seen in children and usually associated with displacement of the globe downward and outward as well as with oedema and inflammation of the eyelids, both signs that are not present with Tolosa-Hunt Syndrome. Pseudotumour may be difficult to differentiate from lymphomas and other tumours (Flanders et al. 1989).

Acute rectus muscle palsy as a result of orbital myositis (Pollard 1996) is also closely related to orbital pseudotumour and Tolosa-Hunt syndrome. CT or MRI shows swelling of the affecting muscle, usually the lateral rectus, but occasionally the medial or superior rectus. Muscle involvement has also been observed in Graves ophthalmopathy in infants and adolescents (Uretsky et al. 1989).

Acute rectus muscle palsy as a result of orbital myositis (Pollard 1996) is also closely related to orbital pseudotumour and Tolosa-Hunt syndrome. CT or MRI shows swelling of the affecting muscle, usually the lateral rectus, but occasionally the medial or superior rectus. Muscle involvement has also been observed in Graves ophthalmopathy in infants and adolescents (Uretsky et al. 1989).

The painful ophthalmoplegia of Tolosa-Hunt syndrome may be difficult to distinguish from ophthalmoplegic migraine although involvement of the Vth nerve, increased erythrocyte sedimentation rate and long duration of pain favours the former diagnosis (Kandt and Goldstein 1985). Enlargement of the optic nerve sheath and of the extraocular muscles is also an argument in favour of Tolosa-Hunt syndrome. Treatment with prednisone (1–1.5 mg/day) alleviates the pain and ophthalmoplegia, the latter after several days or weeks but recurrences may occur on discontinuation of treatment or in spite of it. Involvement of the facial nerve is not rare (Swerdlow 1980) with some suggesting that Tolosa-Hunt syndrome may be a form of recurrent cranial nerve neuropathy because of the relative frequency of recurrences that may affect the contralateral side and involvement of different cranial nerves (Barontini et al. 1987).

Cavernous sinus thrombosis may resemble Tolosa-Hunt syndrome when it produces unilateral (and sometimes bilateral) ophthalmoplegia however fever and septic signs are usually marked and there is proptosis and orbital congestion. Vigorous antibiotic treatment is urgently indicated before meningala involvement sets in (Harbour et al. 1984).

CONGENITAL OPHTHALMOPLEGIA

Congenital ophthalmoplegia is often not recognised until relatively late or discounted as representing ‘physiological’ or pathological strabismus. For this reason the diagnosis of congenital ophthalmoplegia should not be excluded on the basis of the child having no ophthalmoplegia at birth by history. Photographs can be extremely useful.

Congenital IIIrd Nerve Palsy

This condition is relatively uncommon, being unilateral in the vast majority. All bilateral congenital IIIrd nerve palsies are associated with additional neurological signs due to anomalous brain development, intrauterine injury (vascular, teratogenic or infectious) and perinatal damage are possible causes.

Congenital IIIrd nerve palsy presents with ptosis, exotropia and hypotropia of the involved eye. The paralysis is generally unilateral and complete although the pupil may be of normal size or even small because of aberrant regeneration: the affected eye is exotropic and usually develops amblyopia. For most individuals evidence of aberrant regeneration is present in the form of lid retraction and/or papillary constriction on attempted adduction (Prats et al. 1993). Cyclic phenomena with spasm of adduction, papillary constriction and lid elevation alternating with adductor paresis, ptosis and papillary constriction may occur. Surgical management of the strabismus involves resection of the medial rectus but is of purely cosmetic value.

Congenital IVth Nerve Palsy

Congenital trochlear nerve paralysis is the most common of congenital ocular motor palsies. There is usually no associated neurological or developmental anomaly but occasionally trauma has been associated (Reynolds et al. 1984). Almost all patients are affected unilaterally (Von Noorden et al. 1986) with the presenting complaint frequently a head tilt away from the paralysed side or even scoliosis. When the head is tilted to the paralytic side hypertropia becomes evident, with surgical therapy it is important to avoid torticollis and scoliosis.
Congenital IVth nerve palsy has been reported with occult cranium bifidum (Bale et al. 1988) and as familial occurrence (Astle and Rosenbaum 1985).

**Congenital VIth Nerve Palsy**

Abducens nerve palsy, rarely seen in healthy neonates, is suspected to be a result of focal damage to the peripheral nerve; often when present it may go unrecognised. Congenital VIth nerve palsies can be unilateral or bilateral and when individuals are affected by the latter this is easily confused with non-paralytic strabismus. It may be a part of Moebius syndrome. The prognosis is typically good, with many children developing binocular vision.

**Congenital Cranial Dysinnervation Disorders**

Duane retraction syndrome is characterised by a palsy of the lateral rectus, limitation of adduction and narrowing of the palpebral fissure due to of globe retraction on attempted adduction. It is the most common congenital dysinnervation disorder (Oystreck et al. 2011) and more often unilateral than bilateral while also attributed to absence or hypoplasia of the abduces nerve with innervations of the ipsilateral lateral rectus muscle by the oculomotor nerve (Breinin 1957; Miller et al. 1982; Miller 1985; Parsa 1998). Interestingly, a majority of children with Duane syndrome are able to maintain binocular vision by turning their head toward the side of the lesion with abnormalities of the brainstem auditory evoked potentials also found (Jay and Hoyt 1980).

Duane syndrome is often associated with additional brainstem anomalies. More complex forms associated with Marcus Gunn phenomenon (Isenberg and Blechman 1983) (see below) or with the ‘crocodile tears’ phenomenon (Biedner et al. 1979) are on record, indicating that the tendency to abnormal synkinesis may be widespread. Crocodile tears are thought to be due to a discrete lesion in the vicinity of the abduces nucleus with innervation of both the lateral rectus and salivary gland by ocular motor fibres. Several different phenotypes have been described, involving a number of different chromosome mutations. For some individuals this may be transmitted as an autosomal dominant condition.

**Fibrosis of Extraocular Muscles (Congenital Familial Externnal Ophthalmpoegia)**

This disorder is characterised by the local (Prakash et al. 1985) or diffuse (Hiatt and Halle 1983) replacement of muscle fibres by fibrous connective tissue and for most individuals affected is dominantly inherited. The only manifestation is restricted ocular motility in the fields of affected muscles while ptosis is generally present. Diagnosis can be made through the biopsy of the fibrotic muscles with the classic type caused by a mutation in the region of chromosome 12q12 (Engle et al. 2007). Several phenotypes of congenital fibrosis have been described (Engle et al. 1994, 2002; Yazdani and Traboulsi 2004).

Brown syndrome differs from congenital fibrosis. The condition is often caused by shortening of the superior oblique muscle or tendon (Walsh and Hoyt 1969) while passive elevation of the globe in adduction is restricted as is voluntary elevation. For some individuals this may occur as a result of rheumatoid arthritis (Wang et al. 1984) or trauma. Surgical treatment can produce cosmetic benefit for patients with muscle fibrosis.

**CONGENITAL PTOSIS**

Congenital ptosis is a common condition caused by absence or fibrosis of the levator palpebrae. This may be congenital although the condition is usually sporadic (Walsh and Hoyt 1969). Seventy per cent of patients are affected unilaterally while ptosis is rarely associated with extraocular muscle involvement. Some patients demonstrate a synkinesis between the movements of the jaw and those of the upper lid such that lowering the jaw or moving it sideways produces elevation of the lid which is especially striking in infants when sucking, the so-called jaw-winking or Marcus Gunn phenomenon (Pratt et al. 1984). An inverted Marcus Gunn phenomenon in which there is drooping of the lid on opening of the mouth has been reported as a congenital (Lubkin 1978) or acquired (Rana and Wadia 1985) phenomenon. The mechanism of this phenomenon may be aberrant regeneration but a central mechanism is possible and has also been proposed for other synkineses (McLeod and Glaser 1974).

Congenital ptosis should be distinguished from acquired ptosis and especially from myasthenia gravis. Corrective surgery is indicated for cosmetic reasons or when vision is impaired by the drooping lid.

**GAZE PALSIES**

Gaze palsies are due to involvement of the supranuclear pathways that control the orientation of the head and eyes (Daroff and Troost 1978). Such control is integrated at several levels including the vestibular nuclei, other brainstem structures, the basal nuclei and cerebral cortex (Pierrot-Deseilligny et al. 1997). The diagnosis of supranuclear ocular palsies rests on the characteristics of abnormal head movements and on demonstration that the eyes can move normally in response to the doll’s head manoeuvre, caloric testing and Bell’s phenomenon. The main causes of gaze palsies are listed in Table 22.11 and only some of the manifestations and causes will be discussed here.

**Horizontal Gaze Palsies**

Horizontal gaze palsy may occur sporadically or as part of an hereditary condition. It can be due to a cortical lesion in the
Vertical gaze palsies may be difficult to distinguish from a simple difficulty in looking upwards, which is frequent in patients with mild disturbances of consciousness and even in fatigued patients. Transient disturbances in supranuclear vertical gaze occur in up to 2% of healthy neonates with downward deviation of gaze (Hoyt et al. 1980) which can be associated with upbeat nystagmus (Goldblum and Effron 1994). Yokochi (1991) reported episodes of downward gaze deviation in 13 neurologically impaired preterm or term infants with a history of perinatal asphyxia. These episodes lasted several seconds each during wakefulness with all patients having imaging evidence of periventricular leukomalacia involving predominantly the optic radiations, and half having intellectual disabilities or cerebral palsy at 5 years of age; however, similar episodes with a benign course have also been reported (Kleiman et al. 1994).

Ouvrier and Billsom (1988) reported a syndrome which they termed benign paroxysmal tonic upgaze of childhood, characterised by episodes of sustained tonic conjugate upward deviation of the eyes, lasting from 30 minutes to several hours, with compensatory forward bending of the head. On attempted downward gaze downbeating ocular saccades would occur with fluctuating symptoms increased by fatigue and intercurrent illnesses and relieved by sleep. The onset was between 6 and 24 months of age with affected children having no other difficulty except mild ataxia. All symptoms spontaneously disappeared in a few weeks or months, with similar instances reported by Deonna et al. (1990) and by Guerrini et al. (1998) who also mentioned the occurrence of occasional atomic falls. Very similar symptoms but with an earlier onset in the first month of life have also been described (Ahn et al. 1989). The syndrome has, in various instances, been reported as inherited from family and the episodes of downward gaze can be abolished by low-dose-L-dopa treatment, suggesting a possible link to dopa-sensitive dystonia (Campistol et al. 1993). Association with psychomotor retardation has been rarely reported (Sugie et al. 1995).

However, recent work (Hertle et al. 1998) indicates a less favourable outcome with respect to both cognition and fine motor control.

Paralysis of vertical gaze that has been described in intoxication with anticonvulsants, antidepressants and other drugs may be explained in part by the disturbance of consciousness, but this does not apply to all patients and true ophthalmoplegia has been repeatedly observed.

The most important cause of vertical gaze palsy is represented by tumours in the pineal region. The sylvian aqueduct syndrome can also be seen in patients with hydrocephalus due to aqueductal stenosis. The syndrome features associated eyelid retraction, mydriasis with dilated pupils with better contraction to near objects than to lights (light-near dissociation), skew deviation of the eyes and sometimes convergent-retractive nystagmus (nystagmus retractorius) and disturbances in horizontal gaze. The pretectal syndrome has been reviewed in detail by Keane (1990). Disorders of the basal ganglia such as Huntington disease are frequently associated with vertical supranuclear gaze palsies while vertical downward gaze palsy is also a feature of Niemann-Pick and Gaucher diseases and is a key clinical feature of Niemann-Pick type C disease (Salsano et al. 2012). In the latter paralysis, horizontal gaze

### Table 22.11 Types and causes of gaze palsies

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DAF, downward gaze palsy, ataxia and foam cells.
Part IX  Disorders of the Oculomotor, Visual, Auditory and Vestibular Systems

Disorders of the Oculomotor, Visual, Auditory and Vestibular Systems

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is frequently associated (Grosse-Tsur et al. 1989) and may be isolated (Patterson et al. 1993).

Keane and Finstead (1982) have reported that isolated upward gaze palsy may be the initial manifestation of the Miller Fisher syndrome and Sandyk (1984) has described the same phenomenon in vitamin B12 deficiency.

Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia is characteristic of the involvement of the medial longitudinal fasciculus which prevents transmission of influx from the pontine centre for lateral gaze (para-abducens nucleus in the paramedian pontine reticular formation: PPRF) to the contralateral IIIrd nerve nucleus, resulting in disconjugate lateral gaze. In unilateral lesions of the medial longitudinal fasciculus, the internuclear ophthalmoplegia is also unilateral. There is usually associated nystagmus of the abducting eye.

Figure 22.9  Internuclear ophthalmoplegia. On attempted gaze to either side, there is no contraction of the internal rectus, due to involvement of the medial longitudinal fasciculus which prevents transmission of influx from the pontine centre for lateral gaze (para-abducens nucleus in the paramedian pontine reticular formation: PPRF) to the contralateral IIIrd nerve nucleus, resulting in disconjugate lateral gaze. In unilateral lesions of the medial longitudinal fasciculus, the internuclear ophthalmoplegia is also unilateral. There is usually associated nystagmus of the abducting eye.

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Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia is characteristic of the involvement of the medial longitudinal fasciculus that connects the abducens nucleus on one side and opposite ocular motor nucleus to permit conjugate lateral gaze (Fig. 22.9). When these nuclei are disconnected attempted lateral movements produce abduction of the eye ipsilateral to the fasciculus lesion and absence of the normal adduction of the contralateral eye. The phenomenon may be uni- or bilateral and is mainly due to multiple sclerosis although in children brainstem tumours and head trauma may be a more frequent cause (Mueller et al. 1993). Other causes such as metabolic, immunological and inflammatory processes have been associated. When the disorder is mild contraction of the medial lateral rectus may be present but slower than that of the lateral rectus, while nystagmus of the abducting eye is usually present. The ‘one-and-a-half syndrome’ is a variant characterised by complete lateral gaze palsy to one side (‘one’) with contralateral paralysis of the adduction (‘and-a-half’). It is caused by a lesion involving the parapontine reticular formation and the longitudinal fasciculus on the same side (Pierrot-Deseilligny et al. 1981; Wall and Wray 1983).

Convergence Palsy

Convergence palsy is an inability to adduct both eyes in the absence of medial rectus paralysis with the most common cause probably closed head injury (Krohel et al. 1986) and other factors including stress and fatigue (van Leeuwen 1999); convergence palsy may be encountered even following minor head trauma. Before making the diagnosis it is necessary to rule out the presence of a tumour of the quadrigeminal plate of neighbouring structures. In such instances patients may have a complete insufficiency to converge. Treatment of post-traumatic convergence palsy consists of convergence exercises and/or wearing prisms.

Oculogyric Crisis

Oculogyric crisis is an idiosyncratic reaction leading to restlessness, agitation, malaise or a fixed stare. Typically there is extreme and sustained upward deviation of the eyes which may converge, deviate upward and laterally or deviate downward. There are many drugs commonly used in paediatrics that can trigger an oculogyric crisis including neuroleptics, carbamazepine, diazoxide, metoclopramide and domperidone.

REFERENCES


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Part IX Disorders of the Oculomotor, Visual, Auditory and Vestibular Systems


Disorders of Auditory and Vestibular Function

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Disorders of Auditory and Vestibular Function

Anne O’Hare

Hearing impairment is defined as sensorineural when it arises from abnormalities of the inner ear and cochlear nerve, conductive when it is related to disease or deformity of the outer and middle ear, and mixed if both sets of structures are involved. Sensorineural hearing loss can also be of central origin if it results from abnormalities of the central nervous system (CNS) that subserve audition but lie rostral to the cochlear nerve.

The World Health Organization (WHO) defines a hearing impairment on the basis of the residual hearing in the better ear averaged over 0.5, 1, 2 and 4kHz (WHO 1991) as follows: slight 26–40dB hearing loss (HL), moderate 41–60dB HL, severe 61–80dB HL and profound ≥81dB HL.

Hearing impairment can be further classified on the basis of the age at detection and aetiology. Congenital impairment refers to a hearing impairment that has been recognised at birth or that is believed to have been present since birth. Progressive impairment is one that may become evident either at birth or postnatally, or that worsens over time. A hearing impairment may also have a late onset, but the term ‘acquired impairment’ is reserved for those patients in whom there is an identifiable exogenous cause.

Most countries deliver neonatal hearing screening, with universal screening detecting 69% of significant hearing loss by the age of 6 months compared with 12% in targeted screening (Wake 2005). However, not all hearing impairment will be present in the neonatal period and therefore a high index of suspicion must be exercised during paediatric neurological practice, even for children who have been receiving this screening. It is important to be familiar with your local methods and pathways (Watkin 2012). Fortnum et al. (2001) reported a UK prevalence of 0.91 per 1000 (95% confidence interval [CI] = 0.85–0.98) for 3 year olds, rising to 1.65 (95% CI = 1.62–1.68) for children aged 9–16 years. Around half of the overall prevalence is, therefore, contributed by these older children whose problem is detected after the age of 3 years; they must make up those with congenital impairment who had missed neonatal hearing screening or were false negatives, as well as children who have acquired impairment or developed their impairment postnatally. The latter include children affected by genetic impairments that have a late onset.

Many children seen in neurological practice have experienced an adverse perinatal course and such factors now account for 27% of the childhood population with significant hearing loss, a much higher prevalence rate than that described over 20 years ago. If one takes into account neonatal intensive care unit (ICU) experience, combined with a family history of hearing loss and craniofacial abnormalities that were noticeable at birth, around two-thirds of all types of hearing loss can be identified.

In addition, 30–40% of children with a confirmed hearing loss have developmental delays or other disabilities. Chromosomal abnormalities are associated with the sensorineural hearing loss in around 5% of hearing-impaired children. At the molecular level of aetiology it is salutary to reflect that 1% of the approximately 30 000 or more human genes are necessary for hearing. Many genetic conditions that are associated with hearing impairment are syndromic, although this may not be immediately evident clinically because the wider implications of the disorder are not initially recognised.

The genes implicated in sensorineural hearing loss cover a wide range of processes that are also involved in neurological development and function. These include structural genes, transcription factors, tumour suppressors, signal transduction processes such as ion homoeostasis and intracellular transport, and mitochondrial genes responsible for oxidative phosphorylation and energy production. Advances in this field are rapid and increase our understanding of the role of genes and their interaction with environmental factors, which should result in earlier accurate diagnosis and effective treatments for neurological disorders and hearing loss (Smith 2001; Raviv et al. 2010).
HEARING IMPAIRMENT AND SPEECH DEVELOPMENT

Children need to hear all the sounds of speech in order to acquire language. Figure 23.1 shows the frequency range of average conversational speech.

The major contribution to speech intelligibility is made by high-frequency speech phonemes, which contain the least acoustic power. A high-frequency hearing impairment interferes with the recognition of the speech sounds ‘s’, ‘th’, ‘sh’, ‘h’, ‘k’ and ‘t’ because they have primary acoustic energy $>2000\text{Hz}$. It impacts on the perception of fricative phonemes, which make up 50% of the consonant sounds in the English language, and also contribute as linguistic markers to indicate aspects such as grammatical tense, plurals, possession and gender. Even with high-frequency losses $>4000\text{Hz}$ there will be a negative effect because children may not hear plural forms of words in the English language or hear them inconsistently, especially when they are listening to particular voices such as those of women and children. In addition, high-frequency hearing loss may reduce the audibility of low-frequency speech cues. For adolescents and adults, a high-frequency hearing loss does not typically affect speech recognition until the loss involves frequencies $<3000–4000\text{Hz}$. This protection arises because they have already achieved language competence and thus have at their disposal semantic and syntactic cues that help compensate for decreased audibility. In contrast, young children who are acquiring language do not have enough linguistic experience to employ these cues as effectively. It is important also to realise that young, typically developing children who have normal hearing have greater difficulty than adults when it comes to understanding speech in noisy and reverberant environments, and this is the result of developmental factors and inexperience with language exposure. Understanding speech in noise is therefore interfered with further by high-frequency hearing loss. In addition, a lot of a child’s learning is incidental by overhearing the conversations of others, and these opportunities are diminished when a child has a high-frequency hearing loss (Stelmachowicz et al. 2004). The loss of these opportunities for social communication can have far-reaching consequences and, even after aiding, children show delays in ‘mentalising’, which is the ability to impute and understand other people’s thoughts and motives (Peterson 2004).

Hearing impairment has a very early effect on language acquisition. Infants have a capacity to learn a language simply by being exposed to it during the first 6 months of life, before that they are able to use words themselves. By 6 months of age, this exposure has led to language-specific organisation, such that infants have a stronger perception for a native language phonetic pattern, in contrast to the first few weeks of life when human infants show a similar pattern of phonetic perception, regardless of the language environment in which they are born. These findings clarify that fundamental, cognitive, building blocks are in place for language acquisition because of this perceptual process (Kuhl et al. 1992).

THE PERIPHERAL AUDITORY SYSTEM

The peripheral auditory system consists of the external ear of the pinna and external auditory canal, the middle ear and finally the inner ear or cochlea. Conductive hearing loss arises from interference in the passage of sound waves that pass through the pinna and the external auditory canal to make the tympanic membrane vibrate. This movement of the tympanic membrane is mechanically conducted through the middle ear by the three ossicles of the malleus, incus and stapes. The stapes is located within the oval window of the cochlea where its motion transmits sound waves to the fluid-filled inner ear. In the cochlea, this physical stimulus of sound is converted to an electrochemical stimulus, which in turn is transmitted by the auditory nerve to the higher levels of the auditory system. A sensorineural hearing loss can arise from a lesion of the cochlear, the auditory nerve, auditory brainstem, midbrain or cortex. Conventionally, lesions of the central auditory nervous system involve the relay systems of the superior lateral lemniscus, inferior colliculus and medial geniculate body, with a contribution from the reticular formation, cortical and subcortical areas of the Heschl gyrus, planum temporale and sylvian fissure, with the insula and corpus callosum. The central auditory nervous system has extensive interconnections between its structures, which may make it comparatively resistant to expressing symptomatology after impairment (Moore 1991). The cochlea matures in early embryonic life and there is extensive myelination of the auditory pathways, including the inferior colliculus and the medial geniculate body, by the start of the third trimester (Guzetta et al. 2011).

The inner ear consists of the vestibular system and the cochlea and contains the three fluid-filled chambers of the scala vestibuli and scala tympani, which are filled with perilymph, and the scala media, which contains endolymph. The basolateral surfaces of outer hair cells and basilar membrane are bathed in perilymph, which has a composition similar to that of typical extracellular fluids or cerebrospinal fluid (CSF) in that it has a low potassium concentration of around $5\text{mmol/L}$ and a high sodium concentration of around $145\text{mmol/L}$. The endolymph of the scala media contains an unusually high concentration of potassium (around $150\text{mmol/L}$) and a low concentration of sodium (around $1.3\text{mmol/L}$). The cochlea has a resting potential of $+60\text{mV}$ to $+150\text{mV}$ relative to the interior of a cochlear hair cell. Hearing function requires this electrochemical battery, which depends largely on the high concentration of potassium in the endolymph. Tight junctions in the paracellular spaces of epithelial cells maintain these gradients of sodium and potassium ions in the fluid compartments of the inner ear.

The normal human ear has exquisite sensitivity and can perceive sounds over a dynamic range of six orders of magnitude, and discriminate different frequencies with 0.2% precision.
in the range 50–20,000 cycles per second (Hz). Inside the cochlea, the hydromechanical stimulus of sound results in wave movements of the basilar membrane, which supports the organ of Corti with its two types of receptor cells, one row of inner hair cells and three rows of outer hair cells. Inner and outer hair cells transduce the mechanical energy of sound waves into the electrochemical energy of action potentials. The transduction of sound waves into a neural signal is initiated by the physical deflection of the cochlear hair cells, which mechanically opens channels in the hair cells and allows the passive inward flow of potassium ions from the high potassium environment of the surrounding endolymphatic fluid. This high potassium concentration is maintained by active transport through potassium channels which are located in the strial vascular areas at the outer periphery of the coiled cochlear duct.

The cochlea is tonotopically tuned. The base is most sensitive to high-frequency sound and the apex detects low-frequency sound. To achieve this tonotopic sensitivity, the inner ear tunes the basilar membrane at particular positions along its length and also has a narrow band of frequencies to which hair cells, both inner and outer, are tuned at a particular position on the basilar membrane. These frequency-placed properties of the cochlea are copied in a frequency-specific map of cochlear ganglion neurons (Dallos 1992). Some mutant alleles of deafness genes may initially cause pathology in just one area of the cochlea, and this results in a hearing deficit that is restricted to a particular frequency range of the hearing spectrum.

The primary auditory cortex organisation is shaped by exposure to salient acoustic inputs (Chang and Merzenich 2003). In congenitally deaf humans there is poor cochleotopic organisation, but the chronic auditory stimulation that follows the intervention of a cochlear implant produces many aspects of the auditory cortex picture seen after normal activation, and this supports the hypothesis that severe auditory
deprivation extends the window of the ‘critical developmental period’. Mammalian studies also suggest that noise present in a child’s environment has the potential to contribute to auditory- and language-related developmental delays. However, there is no clear evidence that noise-induced hearing loss occurs in infants receiving intensive care, probably because it is these infants who are the most sick and thus spend the longest period of time exposed to high levels of noise in the ICU, and who are also those who have the highest rates of hearing loss from a range of other factors (Wachman and Lahav 2011).

**CLINICAL ASSESSMENT OF HEARING IMPAIRMENT**

During the physical examination of a child with a sensorineural hearing loss, particular attention needs to be paid to height and weight, cranial nerves, shape of the skull and head circumference, and the appearance of the face and ocular region, particularly looking for abnormalities of the scleral colour, the inner and outer canthal and interpupillary distances, palpebral fissure shape and orientation (Bamiou et al. 2000a).

The ears need to be carefully examined for the presence of preauricular tags, fistulae, pits or abnormalities of size, and shape (Alasti and Van Camp 2009). In one study, brainstem-evoked response audiometry was abnormal in 17% of newborn infants with isolated preauricular tags or pits, and behaviour audiometry confirmed a higher incidence of both conductive and sensorineural hearing impairment (Kugelman et al. 1997). As a result of the association of some syndromes of deafness with dermatological conditions, one should look for pigmentation, keratinisation and onychodystrophy of the skin and nails, with any increase in the number and size of fingers and toes. Attention should also be paid to exploring for cleft lip or palate, micro- or retrognathia, the shape of the philtrum and inspection of the neck, looking for branchial remnants and thyroid enlargement.

Developmental examination is important because of the known association of developmental difficulties with hearing impairment.

**Visual and Ophthalmological Examination**

All children with severe or profound sensorineural deafness should have a visual examination soon after diagnosis. Children with multiple disabilities have a greater likelihood of visual impairment. A visual impairment defined as a visual acuity <6/9 (Snellen chart or equivalent), and/or abnormal binocular vision, was found to affect 34.9% of hearing-impaired children, and 10.9% had ophthalmological abnormalities that did not interfere with vision (Armitage et al. 1995). As the deaf child is more dependent on vision for communication and learning, it is important to consider this aspect of the examination. Refractive errors were the most commonly encountered abnormalities. Many abnormalities may be seen on ophthalmological investigation, including salt-and-pepper retinopathy, glaucoma and cataracts as sequelae of congenital rubella syndrome, and choroidoretinitis following congenital cytomegalovirus infection or toxoplasmosis. Dystopia canthorum, heterochromia iridis and hypoplastic iris stroma are clinical features of Waardenburg syndrome. In Alport syndrome, there may be an anterior lenticonus or macular flecks. A range of metabolic disorders associated with hearing impairment includes eye disease, for example, retinitis pigmentosa in Alström syndrome and Refsum syndrome. Electroretinography (ERG) should be considered for any child with a congenital bilateral hearing loss, and there may be early changes of retinitis pigmentosa with abnormal ERG in Usher syndrome type I, with these features arising after puberty in Usher syndrome type II. Usher syndrome type I is associated with severe audiovestibular system deficits, so difficulties in balance can lead to early presentation (Tsilou et al. 2002).

**Investigations**

The investigation strategy for a child with a hearing impairment can be considered at two levels (Wilson et al. 2005). All children with a hearing impairment should have a close exploration for a family history of deafness that includes conducting audiograms of first-degree relatives. It is also important to enquire about metabolic disorders in first- and second-degree relatives, as well as renal, thyroid and cardiac disorders, craniofacial malformations, pigmentary disorders, vision deficits and developmental problems. One needs to enquire about consanguinity and common origin from an ethnically isolated population (Bamiou et al. 2000a, 2001).

Children with sensorineural hearing loss may require computed tomography (CT) of the temporal bones; in addition, a fine-section, high-resolution MRI is required for any cochlear implant candidate to ensure that the cochlear nerve is present. CT of petrous temporal bones involves radiation but will show the bony structures, including the middle-ear ossicles. MRI of inner ears and the internal auditory meati will show soft tissues of the brain, nerves VII and VIII, and the membranous labyrinth including the endolymphatic sac (Held et al. 1998; Tan and Teh 1998; Bamiou et al. 2000b). Children with profound or progressive hearing loss and craniofacial abnormalities are the ones most likely to have abnormal CT findings. This dual imaging must be timely because the cochlear can calcify within weeks of meningitis (Durisin et al. 2010; Caye-Thomasen et al. 2012), making subsequent cochlear implantation technically challenging and possibly unfeasible.

Children should also have electrocardiography (ECG), an ophthalmological examination, urinoscopy for haematuria and, in some cases, testing for a connexin-26 mutation. Clinically available genetic testing is offered for the three genes that cause non-syndromic deafness: GJB2, SLC26A4 and
WFS1. These genes make a substantial contribution to the total genetic deafness mutation load and are relatively easy to screen for (Smith 2004; Thomas et al. 2004).

There may be an indication for level 2 investigations from the history and clinical findings, and there are important associations between neurological disease and hearing impairment, such as in the mucopolysaccharidoses and mitochondrial disorders. Level 2 investigations include serology for congenital infection, thyroid function tests, immunology tests, haematology and biochemistry, metabolic screen, renal ultrasonography, clinical photography, chromosomal studies with consideration for referral to a geneticist and vestibular investigations. Children being referred for a cochlear implant should be screened for metabolic conditions, especially those with an affected sibling, from consanguineous parents or in whom there is a family history of profound hearing impairment, particularly if associated with developmental delay or dysmorphic features. Metabolic screening should include blood gases, mucopolysaccharides and oligosaccharides, amino acids, very-long-chain fatty acids, blood lactate, urine sugar-reducing substances and phytic acid.

The purpose of investigation incorporates establishing the cause of the hearing loss, gathering information that is relevant to the hearing loss management, investigation of coexisting medical problems, establishing a prognosis for the child and family, and in addition informing epidemiology and thus planning for effective hearing loss prevention and surveillance programmes, and assessing how best to meet the needs for managing children with a hearing loss.

**Audiological Assessment**

A wide range of behavioural tests of hearing for typically developing infants aged >6 months is available, which can be adapted for delayed development, provided that the child has sufficient development to cope with the strictures of the testing situation. Behavioural tests of hearing when conducted with precision complement the role of electrophysiological techniques. Behavioural testing includes the distraction test, visual reinforcement audiometry, the performance test for which a child is conditioned to perform a simple action in response to a sound stimulus and pure-tone audiometry. In addition, there is a range of tests of auditory discrimination of speech (Hickson 2002). Although brainstem audiotory tests can be employed to examine speech acoustics, they are not yet in widespread clinical use (Bishop et al. 2011).

Objective physiological measures are more appropriate for detecting hearing impairment in newborn and very young infants, and for children who are unable to cooperate with behavioural testing. These techniques include otoacoustic emission (OAE) testing (either transient-evoked or distortion-product) and auditory brainstem responses (ABRs). These technologies comprise non-invasive recordings of physiological activity which underlie normal auditory function. The two measures are highly correlated with a degree of peripheral hearing sensitivity.

OAEs are sensitive to outer hair-cell dysfunction and testing can detect sensory hearing loss. The recordings are reliable in neonates in response to stimuli and a frequency range >1500Hz. As OAEs are also sensitive to outer-ear canal obstruction and middle-ear effusion, a positive test result can occur in the presence of normal cochlear function but temporary conductive dysfunction. As OAE responses are generated within the cochlea by the outer hair cells, the technique does not detect nerve VIII or auditory brainstem pathway dysfunction. OAE testing, therefore, may not detect infants with auditory neuropathy or neural conduction disorders without concomitant sensory outer hair-cell dysfunction.

In contrast, the ABR reflects activity of the cochlear, auditory nerve and auditory brainstem pathways. The click-evoked ABR is highly correlated with hearing sensitivity in the frequency range 1000–8000Hz. As the ABR is sensitive to auditory nerve and brainstem dysfunction, ABR screening can lead to a positive result in the absence of peripheral (i.e. middle-ear or cochlear) hearing loss, but in the presence of auditory neuropathy or neural conduction disorders in newborn infants.

An audiological test battery to assess the integrity of the auditory system should include OAEs, a measure of middle-ear function, acoustic reflex thresholds, observation of the infant’s behavioural response to sound, and parental reports of emerging communication and auditory behaviours. There should be appropriate measures of middle-ear function including reflectance tympanometry, using appropriate frequency probe stimuli, bone-conduction ABR or pneumatic otoscopy (Joint Committee on Infant Hearing 2000).

**NEONATAL HEARING SCREENING**

Many countries have adopted universal newborn infant screening programmes. Although there is consensus from a number of influential advisory bodies (Joint Committee on Infant Hearing 2000), the long-term effectiveness of these programmes is still being evaluated (Puig et al. 2005). However, studies of language ability, after early detection of permanent childhood hearing impairment through neonatal screening, has confirmed improved receptive language scores, reading and communication skills (Pimperton and Kennedy 2012). The advocates of neonatal hearing screening propose that all infants should have access to hearing screening using a physiological measure, and that infants with confirmed permanent hearing loss should receive appropriate services before the age of 6 months. The target for universal neonatal hearing screening programmes is a permanent bilateral or unilateral sensory or conductive hearing loss averaging ≥30–40dB in the frequency region important for speech recognition at 500–4000Hz. Infants who pass a newborn infant hearing screen, but who have risk indicators for other auditory disorders or speech and language delay, should receive ongoing audiological and medical surveillance. All programmes must be in a position to take forward the care of an infant who has
been identified as having a hearing loss through a screening programme of neonatal newborn infant hearing. The doctor involved must have an appropriate level of competence and would therefore usually be an audiological physician or a community doctor in audiology, or a paediatrician or otolaryngologist with an appropriate level of training.

AETIOLOGY OF SENSORINEURAL HEARING IMPAIRMENT

Genetic Causes

This is a rapidly advancing field, traditionally categorised into syndromic (30%) and non-syndromic (70%) causes (Friedman and Griffith 2003; Nance 2003; Raviv 2010). Although it is still helpful to make this distinction initially clinically, it is important to appreciate that some syndromic conditions may simply appear non-syndromic because the wider manifestations of the disorder have not been recognised, for example, prolonged Q–T intervals in Jervell–Lange-Neilson syndrome, thyroid dysfunction in Pendred syndrome and retinitis pigmentosa in Usher syndrome. At a molecular level, the distinction can also be confusing. Although 50% of non-syndromic sensorineural hearing loss arises from mutations in connexin-26, other connexin genes can have associated abnormalities, for example, dermatological abnormalities with connexin-30 and connexin-31, palmoplantar hyperkeratosis with a dominant G59A allele, mutilating keratoderma associated with the D66H allele, and neurological abnormalities with connexin-32 seen in X-linked Charcot–Marie–Tooth disease. Around 33 recessive, 41 dominant and five X-linked loci have been mapped for non-syndromic genetic deafness. Despite the very large number of loci that have been identified, most instances of genetic deafness are caused by those mutations that involve a single gene from the connexins (Denoyelle et al. 1999).

The connexins are a family of genes that code for the subunits of gap-junction proteins. Gap junctions form when the hexameric hemi-connexins on the surface of two adjacent cells join to form a complete gap junction. The resulting channels permit the flow of ions and small molecules between the cells. The GJB2 gene at the locus 13q12-13 is one of the more commonly clinically available genetic tests for non-syndromic deafness, the others being for SLC26A4 and WFS1 (Smith 2004). These genes make a substantial contribution to the total genetic deafness mutation load and they are relatively easy to screen for. GJB2 at the DFNB1 locus results in autosomal recessive non-syndromic deafness. GJB2 encodes the transmembrane protein known as connexin-26, which oligomerises with five other connexins to form a connexion, which is the constituent component of gap junctions. The severity of hearing loss in connexin-26 gene mutations is extremely variable and cannot be predicted even within families, although it has been shown to be non-progressive in most cases on follow-up into young adult life (Denoyelle et al. 1999). The DFNB1 gene responsible for this recessive, non-syndromic sensorineural hearing loss causes approximately 15% of all infant hearing losses. It is important to consider testing for this common mutation because this will detect 95% of instances in white families who are not consanguineous. If the test is positive, then there is no further requirement for CT, pericholeic washout or investigations for retinitis pigmentosa (Joint Committee on Infant Hearing 2000).

DFNA36 mutation hearing loss is a condition of early onset and rapid progression of dominant non-syndromic deafness (Makishima et al. 2004).

Mutations of several genes that encode for a variety of different myocins, psychoskeletal motor proteins that create tension or facilitate the movement of cell components along actin filaments, are associated with hearing loss: MYO6, MYO7A, MYO1A, MYO1A and MYO3A (Ben-Yosef and Friedman 2003).

The A1555G mitochondrial mutation infers susceptibility to normal doses of aminoglycosides, an example of a situation in which genetic vulnerability combined with environmental risk factors results in sensorineural hearing loss (Bittner-Glindzicz et al. 2014).

GENETIC SYNDROMES

Again, progress in this area is very fast and there are an increasing number of conditions in which the following molecular analysis can confirm diagnosis: Waardenburg syndromes types I–IV, Treacher Collins syndrome, Alport syndrome, branchio-otorenal syndrome, Usher syndrome, Jervell–Lange-Neilson syndrome, Pendred syndrome, Charcot–Marie–Tooth disease and craniosynostosis–deafness. The three syndromes of Jervell–Lange-Neilson, Pendred and Usher may all initially appear to be non-syndromic until the involvement of other organs is recognised.

Prolonged Q–T Syndrome/ Jervell–Lange-Nielsen Syndrome

Mutations in the various potassium channel genes may result in the long Q–T syndrome and, when this is associated with congenital sensorineural deafness it is known as the Jervell–Lange-Nielsen syndrome (JLNS) (Neyroud et al. 1997). The prevalence is 0.21% in children with congenital deafness (Ocal et al. 1997). Prolongation of the Q–T interval is seen on ECG, and reflects a defective cardiac repolarisation that can lead to recurrent episodes of syncope, ventricular arrhythmia and sudden death. Syncope episodes can be precipitated by fright. The long Q–T syndrome is defined on the basis of a QTc (corrected QT) interval >470ms in asymptomatic individuals. The KVLQTT1 gene that causes JLNS also causes Ward–Romano syndrome, in which there is no hearing loss. KVLQTT1 maps to chromosome 11p15.5 (JLNS1 locus);
a recessive mutation involving another potassium channel gene, \( KCNE1 \), at the \( JLNS2 \) locus on chromosome 21q22.1, may produce an identical phenotype which affects the active potassium transport system in the hair cells of the cochlea. Another potassium channel gene, \( KCNQ4 \), which is limited to the outer hair cells, has mutations that cause a relatively common dominant form of progressive hearing loss, which typically begins in the first two decades of life, first involving the high frequencies and then progressing within a decade to profound deafness.

All children with hearing impairment should have ECG, and if marginal or abnormal they should be referred to a cardiologist for further investigation because they may require further monitoring with ECG and exercise testing to establish whether there is a prolonged Q–T interval. This is associated with a high risk of syncope and sudden death during the first year of life or later, and there is also a vestibular areflexia.

Pendred Syndrome

Pendred syndrome, which arises from mutations in \( SLC26A4 \), is the most common cause of syndromic deafness, accounting for more than 5% of all individuals with autosomal recessive hearing loss. It is characterised by bilateral sensorineural hearing loss associated with goitre with or without hypothyroidism (Reardon et al. 1997). There appears to be a relationship between the severity of the hearing impairment and the degree of hypothyroidism. The deafness is congenital and associated with temporal bone abnormalities, which range from isolated enlargement of the vestibular aqueduct to Mondini dysplasia, which is a more complex malformation that also includes cochlear hypoplasia (Napiontek et al. 2004). The hearing loss is usually profound but can be variable in onset, rapidly progressing and unilateral. The goitre generally develops after the age of 10 years, and the thyroid dysfunction is variable. The sensorineural deafness is occasionally associated with disturbed vestibular function.

Usher Syndrome

Usher syndrome affects 2–4% of all patients with profound deafness and 50% of the deaf-blind population. Usher syndrome type I is characterised by vestibular dysfunction, profound congenital hearing loss and early onset of retinitis pigmentosa. The progressive degeneration of the retina results in loss of night vision and restriction of visual fields, leading to blindness. Type I is distinguished from type II by this early onset of retinitis pigmentosa. Type II also has a generally less severe hearing loss and normal vestibular function. Usher syndrome type III is characterised by a progressive postlingual hearing loss and varying severity of retinitis pigmentosa, without a vestibular component. Usher syndrome is phenotypically and genotypically complex with, for example, \( USH1 \) loci mapping to 10q21-22 and 11q13.5 (Ben-Yosef and Friedman 2003).

Alport Syndrome

In Alport syndrome, the hearing loss may not present until the age of 8–10 years, and 50% of those affected have progressive bilateral hearing loss involving high frequencies initially. There is a progressive nephritis. The incidence is one in 10 000 births, and X-linked, autosomal recessive and autosomal dominant varieties occur. Haematuria is seen in the first decade of life, and diagnosis is based on this plus a family history of haematuria or renal failure, characteristic renal biopsy findings, sensorineural hearing loss, and ophthalmic signs of anterior lenticonus or macular flecks. Ocular findings might also include congenital cataracts and spherophakia. The disease results from mutations involving one or other of three tissue-specific polypeptide subunits of collagen that are encoded by the \( COL4A3 \), \( COL4A4 \) and \( COL4A5 \) genes. The \( COL4A5 \) gene is located at Qq22, whereas the genes coding for collagens 3 and 4 are next to each other on 2q35. (See Chapter 26.)

Waardenburg Syndrome

Waardenburg syndrome affects 1–2% of individuals with profound hearing loss, which can be bilateral or unilateral and is associated with defects in tissues and structures derived from neural crest cells (Liu et al. 1995). Pigmentary abnormalities include brilliant blue eyes, complete or segmental heterochromia, and patches of cutaneous hyper- or hypopigmentation. There is lateral displacement of the inner canthi of the eyes, a pinched appearance of the nose and synophrys. Gastrointestinal symptoms can occur, and there may be a history of Hirschsprung disease. There is an increased incidence of neural tube defects and limb defects. There are at least eight loci that contribute to the phenotype. Waardenburg syndrome type I can result from more than 50 different mutations involving the \( PAX3 \) gene on 2q35. Waardenburg type IIA results from mutations at the \( MITF \) locus on 3q12, and this condition has less frequent eyelid anomalies and a higher degree of deafness and heterochromia. Some Waardenburg type IIA patients have albinism, with or without freckling, and this is known as...
Tietz syndrome. A number of other loci have been described such as those in Waardenburg syndrome type III, a condition that features various limb defects. The mechanism here appears to be that the cochlear neural crest cells contributing to the intermediate layer of the stria vascularis are affected and likely to be the cause of the deafness because the stria cannot maintain the critical endocochlear potential that is required for the hair cells to function normally.

**Wolfram Syndrome**

Wolfram syndrome is an autosomal recessive disease characterised by diabetes insipidus, diabetes mellitus, optic atrophy and deafness; it arises from mutations of WFS1. There is high-frequency hearing loss, and the condition can also involve peripheral neuropathy with urinary tract atony and psychiatric illness. A dominant low-frequency sensorineural hearing loss can also be caused by mutations in WFS1 (Lesperance 2003). As routine hearing screening of newborn infants will not typically identify hearing loss affecting frequencies <2000Hz, children at risk of deafness in Wolfram syndrome need to be specifically monitored. (See Chapter 26.)

**Congenital Fixation of the Stapes Footplate with Perilymphatic Gusher**

This is an X-linked syndrome featuring mixed or sensorineural deafness, the conductive component of which involves congenital fixation of the stapes footplate. If attempts are made to mobilise this, there is a profuse flow of endolymphatic fluid. CT shows dilatation of the internal auditory meatus, with abnormal communication between the subarachnoid space and the cochlear endolymph. Carrier females may have a mild hearing loss and a less severe abnormality of the inner ear. The locus maps to Xq21.1; in many families the mutation has been shown to be a deletion, and it can sometimes involve nearby genes for intellectual disability and choroideraemia.

**Syndromic Hearing Loss Associated with Dermatological Disorders**

There are at least five dermatological disorders that are associated with syndromic hearing loss; these also involve a wide variety and severity of organ involvement. An example is the Bart–Pumphrey syndrome, which is an autosomal dominant disorder characterised by sensorineural hearing loss, palmoplantar keratoderma, knuckle pads and leukonychia (Richard et al. 2004).

**Dominant Optic Atrophy, Sensorineural Hearing Loss, Ptosis and Ophthalmoplegia**

This syndrome is caused by a missense mutation in OPA1 (Payne et al. 2004). OPA1 is a nuclear gene but the gene product localises to mitochondria, suggesting that mitochondrial dysfunction might be the common pathway to many forms of syndromic and non-syndromic optic atrophy, hearing loss and external ophthalmoplegia.

**Craniofacial Abnormality Syndromes**

A large number of syndromic conditions with craniofacial abnormalities are associated with deafness, some of which have delineation of the underlying molecular basis of the hearing impairment. An example is branchio-otorenal syndrome, associated with mutations in EYA1 and EYA4 genes affecting transcription factors. This syndrome may have associated Mondini syndrome-type cochlear hypoplasia with hypoplastic and displaced ossicles. Renal ultrasonography may demonstrate agenesis or hypoplasia or dysplasia of the kidneys.

Children with profound or progressive hearing loss and craniofacial abnormalities are more likely to have abnormal CT findings. A dilated vestibular aqueduct correlates with the presence of progressive hearing impairment. CT of the petrous temporal bones has been found to be abnormal in 6.8–12.8% of patients with bilateral sensorineural hearing loss and in up to 30% of cochlear implant candidates. Mondini syndrome-type dysplasia is the presence of a cochlea with a normal basal turn and a distal sac. Semicircular canals are absent or dysplastic in the colobomas, heart defects, atresia of the choanae, retarded growth/development, genital hypoplasia and ear anomalies or deafness (CHARGE) association and in VATER–RAPADILINO syndrome (VATER is the association of vertebral defects, anal atresia/stenosis, tracheoesophageal fistula, radial defects and renal anomalies, whereas RAPADILINO includes radial defects, absent/hypoplastic patellae, high cleft palate, diarrhea and dislocated joints, little size, a long slender nose and normal intelligence, with hearing loss also a feature) (Bamiou et al. 2000a).

**Sensorineural Hearing Loss with Chromosomal Abnormalities**

Chromosomal abnormalities occur in around 5% of children with sensorineural hearing loss. Hultcrantz (2003) reported that 61% of females with Turner syndrome experienced otitis media and sensorineural dip in hearing; in some patients this was observed as early as age 6 years and it progressed over time.

The 6q− syndrome can be accompanied by a bilateral severe sensory hearing loss. This rare disorder, due to a monosomy or trisomy of 6q, results in intellectual disability, microcephaly, asymmetrical face, broad nasal bridge, hypertelorism, epicanthus, strabismus, high arched palate, ventricular septum defect and seizures. Tetraplegia and diaphragmatic hernia have also been described (Schuster et al. 2003).

**Hearing Loss with Neurological Disease**

An inherited disorder of white matter with ataxia, leukodystrophy and sensorineural hearing loss, progressing to complete
deafness by age 12 years, was reported by Leuzzi et al. (2000). Familial cerebellar ataxia with hypergonadotrophic hypogonadism and sensorineural deafness has been described, but generally with the hearing loss developing in adult life (Storey 2001; Georgopoulos et al. 2004).

Children with autism have an increased rate of audiological problems, with one group describing profound bilateral hearing loss in 3.5% of patients (Rosenhall et al. 1999). Discomfort with sound was common, affecting 18% of cases; serious otitis media occurred in 23.5%, with an associated conductive hearing loss in 18.3%.

Prevalence of sensorineural hearing loss of 17.3% has been described in Rett syndrome, and was increased in the older participants and those who had had seizures requiring the use of anticonvulsants in the study by Pillion et al. (2003).

Sensorineural hearing loss may be associated with neurodegenerative disorders, such as Hunter syndrome, and with sensorimotor neuropathy in Friedreich ataxia and Charcot–Marie–Tooth syndrome.

**Refsum Disease**

Refsum disease is characterised by retinitis pigmentosa, anosmia, chronic sensorimotor neuropathy and ataxia. Hearing loss is common, so those patients who report hearing difficulties should have a full audiometric investigation (Bamiou et al. 2003). There is a range of hearing loss types in the condition, varying from mild, predominantly high frequency, to moderate, as well as some evidence to suggest that there may be subtle auditory nerve involvement. Oysu et al. (2001) described the absence of ABRs but the presence of otoacoustic emissions in a patient with Refsum disease and hearing loss. This suggests that the hearing loss might be secondary to auditory neuropathy, with the hearing abnormality determined from the post-outer-hair-cell level. There may therefore be limited benefits and a risk of noise-induced damage to outer hair cells with the use of hearing aids, so the latter should be carefully considered and otoacoustic emission measurements undertaken in individuals with Refsum disease.

**Brown–Vialetto–Van Laere Syndrome**

Brown–Vialetto–Van Laere syndrome is a progressive motor neuron disease accompanied by a sensorineural deafness. Onset is in late childhood or early adulthood, usually signalled by a sensorineural hearing loss which is then followed by other lower cranial nerve involvement (VII–XII), along with lower and upper motor neuron signs in the limbs, and respiratory insufficiency. Usually death followed in 6–18 months but recent advances in the understanding of the condition has implicated the C2orf54 gene located in 20p13; recently there has been some benefit seen in patients after the successful administration of riboflavin (Bosch et al. 2011). Patients demonstrate both familial and sporadic syndromes. Some neurophysiological studies show evidence of nerve damage with subsequent improvement, which raises the possibility that the disorder is caused by primary nerve damage rather than motor neuron disorder (Degrandis 2005; Prabhu 2005).

**Mitochondriopathies**

Co-segregation of the mitochondrial DNA A1555G and G4309A mutations has been described, which results in deafness and mitochondrial myopathy. Symptoms include progressive external ophthalmoplegia, exercise intolerance and deafness after aminoglycoside exposure (Campos et al. 2002). Mitochondrial cytopathies can present with a variety of symptoms, but occasionally sensorineural hearing loss is the first manifestation and some patients have been described who responded well to cochlear implantation.

Sensorineural hearing loss is a common symptom in patients with myoclonic epilepsy associated with ragged-red fibres (MERRF). In this situation pure-tone threshold audiometry can show bilateral, sloping-type, sensorineural hearing loss and the primary lesion appears to be in the cochlea, although there may be some involvement with retrocochlear structures (Tsutsumi et al. 2001).

There is a high incidence (42%) of sensorineural hearing loss in children with mitochondrial encephalopathies including Kearns–Sayre syndrome, Friedreich ataxia and MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes). The hearing impairment is progressive but does not have a prognostic value for understanding the progression of the underlying disorder. Findings suggest that there may be cochlear and retrocochlear involvement (Zwirner and Wilichowski 2001). The histopathology in MELAS has shown that there is severe degeneration of the stria vascularis and degenerative change of spiral ganglion cells which causes the sensorineural hearing loss (Karkos et al. 2005).

**Bioppterin Deficiency**

Three-quarters of affected infants will develop a hearing loss that may be profound and persists even after treatment has been instigated (Wolf et al. 2002). Hearing loss can be completely prevented by presymptomatic diagnosis and the administration of supplemental biotin. (See also Chapter 9.)

**CONGENITAL INFECTIONS**

**Rubella**

Hearing impairment may be an isolated sequel of congenital infection with rubella, but rubella infection is currently very rare in the UK; the National Congenital Rubella Surveillance Programme reported that the incidence of congenital rubella births had fallen to an average of four per year over the period 1991–5 (Miller et al. 1997). Even after a resurgence of infection in the community, only 12 congenital rubella births were reported in 1996 (Tooke and Peckham 1999). However, it
is important to remember that the uptake of vaccine varies across countries, and this can result in cohorts of susceptible women (Crowcroft and Pebody 2004).

Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of sensorineural hearing loss (Boppana et al. 2010). Of all instances of deafness in patients, 20–30% may be caused by CMV, and congenital CMV infection results in sensorineural hearing loss in around a fifth of affected children (Barbi et al. 2003). Half the symptomatic, antenatally infected infants will have neurological manifestations with poor outcomes, and a third will have a bilateral sensorineural hearing impairment (Townsend et al. 2011). Hearing loss may be progressive or fluctuating, and infants will need to be kept under review (Fowler et al. 1997). Therefore, the diagnosis of a sensorineural hearing loss in a child with neurological impairment should always trigger reflection as to whether CMV may be the aetiology for both conditions. Sensorineural hearing impairment is more likely to occur in the presence of a viraemia via cytopathic and immune-mediated processes acting on the organ of Corti (Amir et al. 2011). Sometimes the CMV viraemia can be identified retrospectively, through polymerase chain reaction (PCR) by examining the Guthrie blood spot (Walter et al. 2008), but, as not all children will have a viraemia at all stages of gestation, only the isolation of virus in saliva and urine in the first phase of life is fully confirmatory (Boppana et al. 2010); however, Amir et al. (2011) have argued that the presence of lenticular striatal vasculopathy on neonatal ultrasonography can be a marker of CMV infection that will progress to involve a sensorineural hearing impairment. In that study, children were treated with ganciclovir and valganciclovir with good effect; however, neutropenia with ganciclovir is common, affecting almost two-thirds of treated infants (Kimberlin et al. 2003). (See also Chapter 16.)

Toxoplasmosis

Congenital toxoplasmosis may cause hearing loss (see Chapter 16).

Syphilis

Syphilis can also cause hearing loss in the secondary or tertiary phase, and a positive fluorescent treponemal antibody absorption test assists in diagnosis.

PERINATAL CAUSES OF SENSORINEURAL HEARING LOSS

The prevalence of sensorineural hearing impairment in graduates of neonatal units is 4.9% (D’Amore et al. 2011) and risk factors encompass very low birthweight, assisted ventilation over 5 days, low Apgar scores and exposure to ototoxic medications. Hearing impairment, defined as a loss of >70dB in the better ear before amplification, affects 3% of children with cerebral palsy who were born moderately preterm and 2% of those who were moderately low birthweight (Andersen et al. 2011). The prevalence of sensorineural hearing impairment increases with increasing severity of cerebral palsy (Baird et al. 2011; Reid et al. 2011) and affects up to 6% of children with dyskinetic forms (Himmelman et al. 2009).

Hyperbilirubinaemia

The auditory pathways are especially vulnerable to bilirubin toxicity, which impairs mitochondrial function and viability of astrocytes, and promotes neuronal apoptosis. There may be preservation of cochlear microphonics with abnormalities of the ABRs because bilirubin does not appear to be as toxic to the inner and outer hair cells of the cochlea, although it affects the cell bodies of the auditory nerve in the spiral ganglia and the auditory brainstem nuclei, inferior colliculus and superior olivary complex (Shapiro 2005). There is no clear interrelationship of the level of clinical and biochemical jaundice and the underlying aetiology or the findings on the ABRs in the early stages after kernicterus, and the long-term prognosis (Yilmaz et al. 2001). Therefore, any child who has been exposed to toxic levels of bilirubin merits a comprehensive audiological assessment, with particular care to assess both cochlear and auditory nerve function.

POSTNATAL ACQUIRED HEARING IMPAIRMENT

Meningitis and CNS Infection

Meningitis is the most frequent cause of acquired sensorineural hearing loss in childhood (Watkin 2012). The risk of this sequela is increased with the development of hydrocephalus and/or if the child is aged <1 month or >5 years and the CSF glucose concentration is <2.2mmol/L. Additional risk factors that increase the likelihood of a hearing loss after non-haemophilus bacterial meningitis include duration of symptoms before admission of >2 days, absence of petechiae, CSF glucose level <0.6mmol/L, a Streptococcus pneumoniae infection and ataxia (Koomen et al. 2003). Most commonly there is either a completely flat audiogram or a predominantly high-frequency hearing loss. Brainstem auditory-evoked potentials (BAEPs) from 101 children with bacterial or aseptic meningitis showed a frequency of BAEP impairment of 35% among those with bacterial meningitis, with 31% experiencing hearing loss on discharge, compared with rates of 21% and 14%, respectively, for aseptic meningitis. Most of the BAEP impairment in the bacterial meningitis cases was associated with Haemophilus influenzae infection. Follow-up in this situation with BAEPs is necessary for those children with initially abnormal findings as a small number return to normal and some deteriorate further (Bao and Wong 1998).
Since the introduction of the *H. influenzae* type b (Hib) vaccine, *S. pneumoniae* has emerged as a dominant causative organism of bacterial meningitis in children, and 14% of 79 children with confirmed bacterial meningitis in one clinical series experienced permanent sensorineural hearing loss after confirmed bacterial meningitis (Wellman et al. 2003). Routine inpatient audiological screening of postmeningitic children has been advocated in order to avoid compliance problems with outpatient audiological assessment. High-frequency hearing loss has been described after Epstein–Barr virus infection, and sensorineural hearing loss is an important complication of mumps, with mumps meningoencephalitis increasing this risk (Kanra et al. 2002).

### Ototoxicity: Drug-Induced Hearing Loss

A wide range of drugs is associated with ototoxicity, including antimalarial drugs such as quinine and chloroquine, non-steroidal anti-inflammatories including salicylate and indometacin, loop diuretics including furosemide, chelating agents such as desferrioxamine, and antibiotics including the aminoglycosides and other antimicrobial agents such as chloramphenicol, colistin, erythromycin, minocycline, polymyxin B and vancomycin; these are reviewed by Schacht and Hawkins (2006).

Aminoglycoside ototoxicity occurs sporadically but also within families in association with a mitochondrial DNA (mtDNA) 155A–G point mutation in the 12S ribosomal RNA gene. Transmission of the same predisposing mutation can render individuals susceptible to sensorineural hearing loss after treatment with streptomycin (Fischel-Ghodsian et al. 1997; Gardner et al. 1997). Aminoglycosides can affect the vestibular system or result in destruction of hair cells in the organ of Corti, depending on the type of aminoglycoside.

Ototoxicity to the cochlear or vestibular system can also follow the application of ototopic antibiotic cardrops (Matz 2004).

### Hearing Impairment Associated with Haematological and Immunological Disorders

The prevalence of sensorineural hearing loss is raised in sickle cell disease (Mgbor and Emadi 2004).

High-frequency hearing loss and middle-ear conductive loss have been described in leukaemia and thalassaemia. The thiamine-responsive megaloblastic anaemia, also known as Rogers syndrome, is an early onset, autosomal recessive disorder defined by the occurrence of megaloblastic anaemia, diabetes mellitus and sensorineural deafness (Neufeld et al. 1997).

There are reports of a possible autoimmune-related sensorineural hearing loss, and examination of the erythrocyte sedimentation rate and immunoglobulins with their subclasses, complement studies and autoantibodies may be informative (Bamiou et al. 2000a).

### Ototoxicity from Antineoplastic Chemotherapy and Radiotherapy

Children treated for megaloblastoma, osteosarcoma and neuroblastoma have a greater incidence and severity of hearing loss as a sequela of treatment. Bilateral decreases in hearing were seen in 61% of 67 patients studied by Knight et al. (2005), and their median time to hearing loss was 135 days. The platinum compounds cisplatin and carboplatin are essential components in the chemotherapeutic treatment of a variety of paediatric malignancies. However, platinum agents have adverse effects including ototoxicity and associated permanent hearing loss. This is manifested as bilateral, high-frequency, sensorineural hearing loss and, with continued administration and cumulative dose, the hearing loss tends to increase in severity and progressively spreads to affect hearing at lower frequencies. Hearing loss can also progress after the completion of treatment and this has been reported in 15–20% of patients. Prior or concurrent craniospinal radiation enhances the ototoxicity of cisplatin. Young age at the time of treatment also increases a child's risk for ototoxicity (Knight et al. 2005). In addition to these agents, aminoglycosides and irradiation can adversely affect high-frequency hearing. A progressive hearing loss can occur after stereotactic radiation treatment in the management of posterior fossa tumours (Jackson et al. 2000).

### Neurofibromatosis

Neurofibromatosis type 2 can give rise to a vestibular schwannoma which commonly presents with deafness and is sometimes associated with tinnitus, a facial nerve paralysis or headache. Vestibular schwannomas may be bilateral, and a few selected patients may benefit from auditory brainstem implants. Hearing loss can also occur in neurofibromatosis type 1 (Samii et al. 1997; Cunningham et al. 2005).

### Post-traumatic Hearing Loss

Falls and blows to the head that result in temporal bone fracture can result in hearing loss in >80% of patients. Post-traumatic hearing loss may be related to a post-traumatic perilymphatic fistula, whereas minor head trauma may be associated with a progressive sensorineural hearing loss in the presence of a dilated vestibular aqueduct (Fig. 23.2) (Gopen et al. 2011).

### Conductive Hearing Loss

**Otitis Media with Effusion**

Otitis media with effusion (OME) affects 10–30% of 1–3-year-olds, and by the age of 4 years the cumulative incidence is 80%. By definition, OME involves a middle-ear effusion without signs or symptoms of an acute infection and it is a sequel to acute otitis media. It can result in a conductive hearing loss.
of around 25–30 dB. Children with positive single tests need to begin a period of observation, because it seems that only long-term OME requires treatment (Butler and MacMillan 2001). Therapies offered for OME include decongestants, mucolytics, steroids, antihistamines, and myringotomy as the surgical treatment. A Cochrane Review of treatment efficacy for children who were otherwise typically developing showed that the benefits of grommets was small (Lous et al. 2005). There is also a risk of tympanosclerosis from surgical procedures. A large trial (Paradise et al. 2005) followed children prospectively from the age of 2 months and then assigned those who had persistent middle-ear effusion before age 3 years on a random basis to the insertion of tympanostomy tubes. There was no significant difference at the age of 6 years in the outcome measures of intelligence, language skills, central auditory processing, behaviour and emotion. Measures of intellectual and language ability at the age of 6 are strongly predictive of later academic performance, so the authors concluded that it was unlikely that these children would develop later developmental difficulties. Lous et al. (2005), however, stressed that clinicians need to make decisions about treatment for children who have speech and language delays, developmental difficulties, or defined clinical syndromes on an individual basis because such children have been excluded from the primary studies looking at the effectiveness of treatment of OME.

Conductive Loss From Isolated Anomalies of the Structure of the Ear

There are a number of genetic causes of conductive hearing loss such as the Mondini defect, which is a congenital malformation of the inner ear that is commonly associated with a sensorineural hearing impairment; in some patients it is also associated with CSF otorrhoea or rhinorrhoea and recurrent meningitis. Ossicular chain aplasias are described.

Apert syndrome is associated with craniosynostosis, midfacial malformations, and syndactyly of the hands and feet; it accounts for 4.5% of all patients with craniosynostosis. Congenital hearing impairment affects 3–6% of patients. OME is the most common abnormality, and there is also an increased incidence of congenital ossicular abnormalities, with ossicular chain fixation and congenital conductive hearing loss (Rajenderkumar et al. 2005a, 2005b).

Conductive Hearing Loss Associated with Skeletal Dysplasias

Many different forms of skeletal dysplasia have a conductive hearing loss component (Hilhorst-Hofstee et al. 1997; van den Ende et al. 1998; Brown et al. 2003; De Leenheer et al. 2003; Imani et al. 2003; Vanhovenacker et al. 2003; Visosky et al. 2003; Daneshi et al. 2005; Weekamp et al. 2005). Associated features are variable. The reader is referred to references in Table 23.1 for details.

Although these conditions are rare, it is important to appreciate that the diagnosis may be missed in females who have very mild craniofacial anomalies and whose deafness may be mistakenly attributed to an isolated ossicular deformity (Robertson et al. 1997).

Fanconi Anaemia

Many morphological anomalies affecting the structures of the ear, head and neck are reported in Fanconi anaemia, although they are present in only a minority of patients.
Conductive hearing loss, external auditory canal stenosis and auricular malformation have been described (Santos et al. 2002).

Auditory Neuropathy

The term ‘auditory neuropathy’ describes functional disturbance or pathological change in the peripheral nervous system, although in this situation the exact site of a lesion is not known. Auditory neuropathy is a sensorineural disorder characterised by absent or abnormal auditory evoked potentials and normal cochlear outer-hair-cell function. In auditory neuropathy children show repeatable cochlear microphonic potentials in the absence of click-evoked ABRs. Although the audiometric findings for some children with auditory neuropathy vary significantly, thresholds on behavioural testing range from normal to profound levels. Speech discrimination skills are also very variable, and in one series (Rance et al. 1999) half of the participants showed little understanding or even awareness of speech inputs in both unaided and aided conditions. However, some children who score at significantly impaired levels on a speech discrimination task may benefit from the provision of amplification (Dowley et al. 2009; Breneman et al. 2012). Auditory neuropathy can follow a compromised neonatal course (Madden et al. 2002), particularly in the presence of neonatal hyperbilirubinaemia, and it can also be seen in children who have a family history of childhood hearing loss (Joint Committee on Infant Hearing 2000). Auditory neuropathy can be associated with a loss of myelin. The pathophysiological changes in neural conduction properties associated with demyelination are likely to have a profound effect on auditory evoked responses because they depend on the relatively precise synchronous response of a population of auditory nerve fibres to a transient acoustic stimulus. Auditory neuropathy has been described in Charcot–Marie–Tooth disease type 1 and in osteogenesis imperfecta.

### MANAGEMENT OF SENSORINEURAL HEARING IMPAIRMENT

Permanent childhood hearing impairment can have a devastating impact on communication skills, educational attainments and quality of life, with a resultant high cost to society. Outcomes are improved for children with congenital impairments if they are diagnosed and intervention starts by age 6 months (Fortnum et al. 2001; Kennedy et al. 2006; Pimper ton and Kennedy 2012). Families should expect choice and confidentiality, and communication in their native language, which should include the following: information about childhood hearing loss, the prevalence and effects of early hearing loss, the potential benefits and risks of screening and evaluation procedures, and prognosis and intervention. Hearing aid fitting may be indicated to give the child access to amplified speech. Cochlear implantation for profoundly deaf children continues to be offered at an earlier age of identification. Optimal benefit is seen from early implantation and children are implanted at earlier and earlier ages, dependent on the security of the diagnosis of permanent deafness and technical, surgical and anaesthetic considerations (Sampaio et al. 2011). Children's additional disabilities are no longer seen as a contraindication to implantation; rather it is their ability to be 'mapped' with the implant, that is, their ability to be conditioned to signal a response with the hearing stimuli, that is important. Health, social services and education agencies all need to be associated with early intervention for the child.

The views and interests of individuals who are affected with deafness must be considered when developing policies with regard to the appropriate use of genetic testing and counselling for families who carry the genes associated with hearing loss. The Joint Committee on Infant Hearing (2000) suggested benchmarks and quality indicators of service with comprehensive coordinated services of the infant's home, family, related professionals with expertise in hearing loss, and state and global agencies responsible for provision

| Table 23.1 Conductive hearing loss associated with skeletal dysplasias |
|--------------------------|-----------------|--------------------|
| **Condition**             | **Inheritance** | **References**     |
| Melnick–Needles syndrome  | AD              | Robertson et al. (1997) |
| Oto-palato-digital syndrome type II | XL          | Zaytoun et al. (2002) |
| Autosomal dominant skeletal dysplasia with congenital stapes ankylosis | AD          | Hilhorst-Hofstee et al. (1997), Brown et al. (2003) |
| Cerebrocostomandibular syndrome | AD          | Van den Ende et al. (1998) |
| Teunissen–Cremers syndrome | AD          | Weekamp et al. (2005) |
| Van Buchem disease        | AD              | Vanhoenacker et al. (2003) |
| Cleidocranial dysplasia   | AD              | Visosky et al. (2003), Suba et al. (2005) |
| Dyschondrosteosis         | AD              | De Leenher et al. (2003) |
| Osteogenesis imperfecta   | Various (seven different types) | Imani et al. (2003) |

AD, autosomal dominant; XL, X-linked.
of services to children with hearing loss. Infants referred from
universal neonatal hearing screening should have audiological
and medical evaluations before the age of 3 months. Infants
who are at risk of progressive or delayed-onset sensorineural
hearing loss or conductive hearing loss should have audiological
monitoring every 6 months until the age of 3 years. Early
intervention services need to be designed to meet the indi-
vidualised needs of the infant and the family, and to address
the child’s acquisition of communication with competent
social skills, emotional well-being and positive self-esteem.
Communication support planning needs to consider both a
visual language and other sign systems, as well as auditory oral
communication.

HEARING AIDS
The successful rehabilitation of the deaf child using hearing
aids depends on careful assessment of hearing in all frequen-
cies, individualised hearing aid prescription, and attentive
follow-up and educational support. The primary aim is to
make speech accessible for the child and, if insufficient care
is taken in matching the aid to child’s needs, the aid will
be rejected. Hearing aid technology advances rapidly but it
cannot as yet completely compensate for the damaged human
ear. This is because the mammalian cochlear outer-hair-cell
system is a biologically active process that amplifies in a highly
frequency-selective manner and with almost instantaneous
response (Dallos 1992). The following are two reasons why
an impaired ear cannot have its narrow tuning restored by a
hearing aid: (1) because the outer-hair-cell system responsible
for the tuning is compromised, and (2) because hearing aids
must amplify gain to input signals, and therefore stimulate
the cochlea at moderate and high levels where tuning is no
longer narrow, even in a normal ear. This means that even the
narrower span compression system will still produce broader
than normal excitation in an impaired ear.

Digital hearing aids have superseded analogue aids because
they are able to take a signal from a microphone and convert
it into numerical data, which can then be manipulated by a
computer within the hearing aid to give a tailored match of
the aid to the hearing loss of the child. They can be worn
behind the ear or within the ear canal or on the body. There
are also bone-conduction hearing aids for people with con-
ductive hearing loss or who cannot wear a conventional hear-
ing aid, where the sound is delivered through the skull by
vibration (Trine and Van Tasell 2002).

INDUCTION LOOP AND INFRARED SYSTEMS
The loop system helps deaf people who use a hearing aid or
loop listener to hear sound more clearly, by reducing or cut-
ting out background noise. Anyone sitting in an area of loop
can pick up the sound if they switch their hearing aid or loop
listening aid to the T setting. Electrical equipment and wiring
can cause interference. As an alternative, an infrared system
be fitted; infrared receivers are not usually prone to inter-
ference, unless they are in direct sunlight.

RADIO-MICROPHONE SYSTEMS
These systems are designed for use in classrooms or similar
settings and they can help deaf learners hear the teacher or lec-
turer from a distance. Learners will need to be wearing hearing
aids to benefit from them, and some systems also work with
cochlear implants. The lecturer wears a clip-on microphone
and the deaf learner wears the receiver. There is no evidence
to support the use of radio-microphone systems for children
with central auditory processing disorders.

SOUNDFIELD SYSTEMS
A soundfield system amplifies the teacher's voice at a low
level and distributes it around the room from speakers
mounted above head height. Deaf learners seated anywhere in
the room will be able to hear equally well.

COCHLEAR IMPLANTATION
In cochlear implantation the sensory organ of the ear is
replaced by an implantable electronic prosthesis. This cochlear
implant stimulates the auditory nerve by electrical pulses and
thus generates the sensation of hearing along the auditory
pathway. In cochlear implants, the electrical signal provided by
the device bypasses the portion of the auditory pathway linked
to internal hair cells and the synapse to the auditory nerve
fibre, and stimulates the spiral ganglion cells directly. Cochlear
implants in prelingually deaf children permit improved devel-
opment of speech reception, language acquisition and reading
comprehension (Rubinstein 2002; Francis and Niparko 2003;
Ramsden 2004).

Cochlear implantation is an effective intervention for the
acquisition of speech perception and verbal language for chil-
dren with severe-to-profound hearing impairment (Francis
and Niparko 2003; Ramsden 2004). Early identification of
the hearing loss, early hearing aid use, and language interven-
tion and cochlear implantation by 2 years of age are positive
predictors for language acquisition, which can even approach
the levels of normal hearing children. Although implantation
of children under age 2 years is potentially associated with
higher surgical and anaesthetic risk, many results have been
very positive (Rubinstein 2002). A late age of implantation
does not preclude beneficial development of vocabulary
(El-Hakim et al. 2001). Variations in the temporal bone anat-
omy in some patients such as those with the CHARGE associ-
ation can give increased technical challenges and an increased
risk to the facial nerve during cochlear implantation. Cochlear
implantation in children with inner ear malformations
can give rise to complications such as CSF leak, but can be a successful method of rehabilitation (Woolley et al. 1998). Children who have their hearing loss identified by the age of 6 months have been demonstrated to have significantly better language scores than children identified after this period (Yoshinaga-Itano et al. 1998; Kennedy et al. 2006; McCann et al. 2009).

**PROGNOSIS OF HEARING IMPAIRMENT**

Studies from animal models and patterns of infant language acquisition suggest that early intervention with aiding is important in hearing impairment. However, the literature also suggests that there are other important factors that influence prognosis. A report from a geographical cohort of intellectually normal children, who had undergone neonatal screening for high-risk infants, revealed outcomes were related to the severity of the hearing impairment and the non-verbal IQ rather than the age of diagnosis (Wake et al. 2005).

It is important to consider that up to 40% of children with a confirmed hearing loss have developmental delays or other disabilities. These need to be taken into account in the evaluation of a child who is failing to show the development of speech production that might be otherwise expected after successful aiding. Speech perception abilities of both cochlear implant and hearing aid users suggest that the performance of an average implant user is similar to that of a hearing aid user with a hearing loss of 70–90dB. Cochlear implantation in infants between the ages of 6 and 18 months can give a good outcome, with prelexical babbling correlating significantly with the age of implantation (Schauwers et al. 2004). Speech and language proficiency is greater for children who had exhibited normal hearing for even a short period after birth and who received their cochlear implant shortly after losing their hearing (Geers 2004). Improvements in speech can continue over many years; 6 years after cochlear implantation, a child’s speech acquisition process is incomplete and there is no evidence of a plateau in performance, with the mean number of intelligible words per utterance increasing from 0.15 to 4.2. In children exposed to aural/oral communication rehabilitation, the age at implantation is an important variable affecting the level of speech production achieved by prelinguistically deaf cochlear implant users. The percentage of intelligible syllables shows a dramatic improvement in intelligibility in the first 3 years after implantation (Blamey et al. 2001). As children with additional disabilities are increasingly admitted to cochlear implantation programmes, there is an increasing challenge to truly capture outcome in the sense of a meaningful improvement in their quality of life because some children may not develop oral communication with speech as a result of their additional impairments (Rafferty et al. 2011). The International Classification of Functioning, Disability and Health (ICF) framework should include understanding outcome in terms of activities and participation in components such as listening and conversing within groups of people (Danermark et al. 2010).

**CENTRAL AUDITORY PROCESSING DISORDERS**

Central auditory processing disorder (CAPD) is an inability or impaired ability to attend to, discriminate, recognise, remember or comprehend information presented through the auditory channels, even though the person has normal intelligence and hearing sensitivity (Keith and Pensak 1991). Functionally, a child with CAPD shows a range of difficulties with the following: the localisation of sound; binaural synthesis, in that stimuli presented simultaneously or alternately to opposite ears are incompletely perceived; and figure ground difficulties in which a primary signal or message is difficult for the child to perceive in the presence of competing sounds. In addition there are problems with binaural separation, memory for auditory stimuli, forming words out of separately articulated phonemes, discriminating two acoustic stimuli, perceiving whole words or messages when parts are omitted, showing listening attention over a reasonable period of time, associating correspondence between a non-linguistic sound and its source, and establishing a correspondence between the linguistic sound and the meaning.

Children with CAPDs show behavioural symptoms with the following: inconsistent responses to auditory stimuli; requests that information be repeated; poor auditory attention; difficulty listening if there is background noise; easy distractibility; problems with phonics and discrimination of speech sounds; poor auditory memory; and poor development of spoken and written language skills (Gordon and Ward 1995).

CAPDs would arise from situations in which information from the cochlear nucleus in the brainstem is affected when relaying to the auditory cortex or subsequently when handled by the cortical and subcortical auditory areas so that audition can be fully appreciated and interpreted. Two main areas of controversy in the concept of CAPDs relate to how best to assess the symptomatology and avoid misinterpretation. When, for instance, the primary reason for the child’s presentation lies with an intellectual or attentional deficit (Howard et al. 2010; Moore et al. 2010), and how best to objectively measure the degree of processing dysfunction.

This is exemplified by work comparing measures of listening and cognition between children with dyslexia and those diagnosed with an auditory processing disorder through audiology departments, in which there were insufficient differences to assign the children to these diagnostic groupings, and features from either group suggested that some children had social communication and interactional difficulties implying that they should be assessed for autistic spectrum disorders (Dawes and Bishop 2009). Also, children may have a common aetiology, such as hypoxic damage, that has resulted in impairment to the auditory nuclei, brainstem and cerebral
Dysfunction of the Vestibular System

Vestibular Testing

Vestibular function testing can be a useful adjunct to audiometric evaluation, even in infants and young children, provided that the testing environment is rendered appropriate (Phillips and Backous 2002). Study of optokinetic and caloric nystagmus can be informative in children presenting with acute vertigo, and significant vestibular hyperreflexia can be demonstrated some time after disease onset (D’Agostino et al. 1999). Young children with idiopathic spontaneous recurrent episodes of vertigo should have an audiogram in addition to vestibular testing (Brantberg et al. 2012).

Electro- and video-nystagmography reveal spontaneous vestibular nystagmus and benign paroxysmal positional nystagmus in children with episodic vertigo. The former is considered to be a sign of a vestibulopathy and the latter is associated with benign paroxysmal positional vertigo. In a series of 34 children aged 4–18 years with episodic vertigo four had bilateral sensorineural hearing loss in low frequencies; in addition, unilateral caloric responses were diminished in eight children (Uneri and Turkdogan 2003). Benign paroxysmal positional vertigo (BPPV) is a labyrinthopathy that results in postural imbalance and brief episodes of vertigo precipitated by specific movements. The symptoms can be secondary to shifting of otoloids in the semicircular canal and, although it is rare in children, it should be recognised because it may be demonstrated only by a particular diagnostic test such as the Dix–Hallpike manoeuvre, which is a diagnostic test for posterior semicircular canal BPPV. Liberating manoeuvres may lead to the mass being removable through the non-ampullary hemicanal (Marcelli et al. 2006).

Patients who have experienced vestibular symptoms associated with migraine headache in so-called vestibular migraine frequently have abnormal caloric test responses, especially with a directional preponderance, and often have spontaneous nystagmus. The hypothesis is that the patients are considered to have hypersensitivity of the labyrinth, presenting with nausea and vomiting, and in the headache-free period the electronystagmography is almost normal (Szirmay 1997). The function of the inferior vestibular nerve and oto-lithic function can be assessed by measuring the vestibular evoked myogenic potentials in the healthy newborn infant (Bamiou et al. 2001).

Peripheral Vestibular Dysfunction

Peripheral vestibular problems in childhood present with a wide spectrum of symptoms, varying from a short episode of dizziness to a typical vestibular attack with vertigo and its sensation of rotation, accompanied by nausea and vomiting (Choung et al. 2003). Symptoms may be precipitated or increased by a changing position of the head or rapid movement. The presentation may require very careful delineation because it can be difficult for young children to describe the subjective phenomena of tinnitus that they might experience in Ménière disease (Miyahara et al. 2009; Brantberg et al. 2012), and sometimes there are particularly unusual symptoms such as vertigo and disequilibrium induced by sound. The latter can occur in dehiscences of the superior semicircular canal, confirmed with CT of the temporal bones, and surgical resolution can be beneficial (Minor et al. 1998). Weisleder and Fife (2001) reported the outcome for a series of children referred for vestibular testing after a presentation with a combination of dizziness and headache, with other symptoms including episodes of loss of consciousness, poor balance and
blurred vision. The most common abnormal test outcome was a unilateral vestibular dysfunction, followed by bilateral peripheral vestibular dysfunction. Central vestibular dysfunction was seen in only one of the 31 children. Final diagnoses included vestibular migraine, benign paroxysmal vertigo of childhood, anxiety attacks, Ménière disease in two children, and one patient with idiopathic sudden-onset sensorineural hearing loss and one with familial vertigo–ataxia syndrome; in a small number of patients no definitive diagnosis was established. Unilateral vestibular hyporeflexia is not exceptional in the child referred for vestibular testing. A considerable number of these vestibular problems might be related to migraine syndromes (Uneri and Türköğlu 2003). Also, children who complain of vertigo or dizziness, but have normal clinical neurological and vestibular examination, should have a complete ophthalmological examination (Anoh-Tanon et al. 2000). Vertigo can be caused by a perilymphatic fistula, with a good outcome after surgery (Weber et al. 2003).

As the cochlear and vestibular organs are closely related anatomically and developmentally, vestibular function may be impaired in sensorineural hearing impairment, particularly that after bacterial meningitis, and can be temporarily disturbed in around 20% of individuals after cochlear implantation (Vibert et al. 2001).

**Toxic Causes**

Many drugs that have the potential to affect auditory function, such as the aminoglycosides, can also have an adverse effect on vestibular function. Antibiotics can produce disturbance in the labyrinth, and the vestibule is particularly vulnerable to toxicity from streptomycin. Vestibular dysfunction can also follow the use of anticonvulsant medication such as phenytoin.

**ACUTE LABYRINTHITIS**

The differential diagnosis of vertigo in children is extensive, and otitis media and middle-ear effusion may be the most common cause with the development of an acute serous labyrinthitis (Tarlow 1998; Goldstein et al. 2000).

Acute labyrinthitis is also an important sequela of acute bacterial meningitis. Infection spreads from the meninges via the cochlear to the inner ear and can result in serous labyrinthitis or suppurrative labyrinthitis. Sensorineural hearing loss may result from damage to the cochlea but in some patients spiral ganglion cells in the retrocochlear region are severely degenerated (Merchant and Gopen 1996).

Acute labyrinthitis can also be virally mediated, and particularly in preschool children can result in episodes in which they are rendered suddenly ataxic in the context of a self-limiting illness that lasts no more than a few days.

Labyrinthitis can occur in association with acoustic schwannoma (Held 1998; Tan and Teh 1998).

**MIGRAINE EQUIVALENTS**

Paroxysmal vertigo is discussed in Chapter 21. Vertigo and headache occur in vestibular migraine and benign paroxysmal vertigo (Weisleder and Fife 2001).

**EPILEPSY AND VERTIGO**

Rotational vestibular epilepsy has been described arising from a focus in the temporoparieto-occipital junction (Altay et al. 2005). A more detailed description of related seizure semiology can be found in Chapter 16.

**VESTIBULAR NEURONITIS**

Infection with *Borrelia* sp. in Lyme disease is a very rare cause of sudden-onset sensorineural hearing loss and vestibular neuronitis (Walther et al. 2003; Ergul et al. 2006). Vestibular neuronitis results in acute episodes of severe vertigo with complete loss of unilateral caloric response. There may be complete recovery of the function of the affected vestibular nerve, or a partial recovery, or indeed no recovery of the affected vestibular nerve but CNS compensation for the vestibular imbalance.

**MÉNIÈRE DISEASE**

Ménière disease is a disease of the inner ear, characterised by a triad of presentations with vestibular symptoms, auditory symptoms and pressure. The pathophysiology of the symptoms is disputed but an endolymphatic hydrops is described and may involve a deficiency in the absorption of endolymph. Typically it is a disease of adults (Da Costa et al. 2002), although it has been described in children (Rodgers and Telischi 1997; Choung et al. 2003). Ménière disease was the aetiology of vertigo in 2.9% of children, and they may describe tinnitus (Akagi et al. 2001).

**POST-TRAUMATIC VERTIGO**

Acute vertigo may follow trauma to the labyrinth and may go on to take a chronic or fluctuating course. Vestibular symptoms with disequilibrium have been described in 50% of patients who sustained otological injuries after inflation of airbags used to mitigate against injury severity in road traffic accidents (McFeely et al. 1999). Hearing loss can also fluctuate and be progressive, or even suddenly deteriorate after a head injury, but its relationship to the common finding of enlargement of the vestibular aqueduct and endolymphatic sac (reported in 5–15% of children with permanent childhood hearing impairment) remains unclear (Gopen et al. 2011).

**BASILAR ARTERY DISEASE**

The sacculocollic reflex is a descending pathway that traverses the territory of the basilar artery and can, therefore, be
implicated in basilar artery migraine and basilar artery cerebral vascular disease. Vestibular evoked myogenic potentials indicate reversible ischemia in the territory of the basilar artery, and patients may show abnormal eye tracking tests on electroneystagmography, with abnormal optokinetic nystagmus testing and abnormalities of caloric testing (Liao and Young 2004).

REFERENCES


PART X
Neuromuscular Diseases

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Diseases of the Motor Neuron

Mariacristina Scoto and Francesco Muntoni

Motor neuron diseases are neurological disorders characterised primarily by the degeneration of spinal motor neurons, skeletal muscle atrophy and weakness, as well as debilitating course with often fatal motor dysfunction. Motor neuron diseases can occur at different ages from infancy to adulthood, are genetically heterogeneous and follow very diverse disease courses from a fatal course in infancy to conditions compatible with normal survival into adulthood. The spinal muscular atrophies (SMAs), originally described in the early 1890s by Werdnig and Hoffman, comprise a group of autosomal-recessive disorders characterised by progressive degeneration of the lower motor neurons. Since their first description several SMA types have been described based on age at onset and predominant clinical features with the most common types acute infantile (SMA type 1, or Werdnig-Hoffman disease), chronic infantile (SMA type 2), chronic juvenile (SMA type 3 or Kugelberg-Welander disease), and the less prevalent adult onset (SMA type 4) forms. The genetic defect associated with these SMA variants is localised on chromosome 5q and due to homozygous deletions or mutations involving the survival motor neuron \( SMN1 \) gene. Neighbouring \( SMN2 \) gene(s) can in part compensate for the absence of \( SMN1 \) genes and there is a correlation between the \( SMN2 \) copy number and the severity of the disease, as will be discussed below. Optimal standards of care have been proposed and have improved significantly the outcome of types 2 and 3 SMA and are also shifting survival in SMA type 1.

There are other inherited motor neuron disorders not caused by mutation of the \( SMN1 \) gene and these, often referred to as non-5q SMA, can also present with early degeneration weakness but different clinical symptoms from classic chromosome 5q-linked SMA. In this chapter we will review the most common forms of SMA focusing on their diagnosis, treatment and management issues, the effect of optimal standards of care on survival and the most recent experimental therapeutic approaches.

**CHROMOSOME 5-PROXIMAL SPINAL MUSCULAR ATROPHY**

The term spinal muscular atrophy refers to a group of genetic conditions characterised by degeneration of the anterior horn motor cells and resulting in muscle atrophy and weakness.

The most common SMA is caused by mutations of the Survival Motor Neuron 1 gene (\( SMN1 \)) on chromosome 5 (5q11.2-13.3) (Brzustowicz et al. 1990; Melki et al. 1990; Lefebvre et al. 1995). This type of SMA was originally described in 1891 in two infant brothers with onset of weakness at around 10 months by Guido Werdnig (Werdnig 1891), followed by seven more individuals described by Johan Hoffman between 1893 and 1900 (Hoffmann 1893, 1897, 1900) while a milder form of the disease in which patients could achieve the ability to walk was described in 1956 by Kugelberg and Welander (Kugelberg and Welander 1956). All these descriptions had a common pathology characterised by anterior horn cells degeneration leading to specific clinical features characterised by symmetrical muscle weakness (proximal more than distal) of the limbs (lower limbs more than upper limbs) together with axial, bulbar and intercostal weakness. The multiple phenotypes were eventually formalised into a classification scheme at an International Consortium on Spinal Muscular Atrophy sponsored by the Muscular Dystrophy Association in 1991. This classification highlighted three SMA types based on the highest level of motor function (i.e. sitting or standing) and age at onset. Subsequent modifications divided the type 3 category by age at onset, adding a type 4 for adult-onset cases and including a type 0 for patients with prenatal onset and death within weeks (Table 24.1) (Munsat and Davies 1992).

**SMA TYPE 1 (SEVERE, INFANTILE OR WERDNIG-HOFFMAN DISEASE)**

Patients with SMA type 1 present between birth and 6 months of age with progressive muscular weakness affecting the lower limbs more than the upper limbs, poor head control and hypotonia as showed by the typical ‘frog-leg’ posture assumed when lying supine, as well as the ‘slip through’ on vertical suspension. There is also weakness in the intercostal muscles with relative sparing of the diaphragm clinically evident.
in the ‘bell-shaped’ chest and paradoxical breathing pattern. Patients also have tongue fasciculations and eventually show bulbar weakness with difficulty swallowing, risk of aspiration and failure to thrive. There is no involvement of other cranial nerves, however facial weakness can develop during the late stage of the disease, while tendon reflexes are invariably absent. Cognition is typically normal and infants often have a bright and alert expression that contrasts with the general weakness.

Within SMA type 1 at least three clinical subgroups can be defined according to the severity of clinical signs:

1a Severe weakness since birth/neonatal period, head control never achieved;
1b Onset of weakness after the neonatal period but generally within 2 months with head control never achieved;
1c Onset of weakness after the neonatal period but head control achieved. A small proportion of children with SMA1c may be able to sit with support indicating a blurred boundary between type 1 and type 2 SMA, which was also highlighted in previous articles in which a decimal classification was proposed (Dubowitz 1995a; Bertini et al. 2005).

SMA type 1 is a very severe condition in which the affected infants are at risk of severe chest infections with acute respiratory failure and usually die before the second year of age (Dubowitz 1995b; Darras 1997) although there has been increase in survival with using assisted ventilation and feeding support (Zerres and Thomas and Dubowitz 1994; Davies 1999; Oskoui et al. 2007). Noninvasive ventilation can be used at a very young age, as early as the neonatal period, because interfaces are now available for small infants (Simonds 2007). Bilevel positive airway pressure ventilation can be provided at home with a face mask enabling the introduction of noninvasive ventilation while the infant is still in relatively good health. As weakness progresses the requirement for ventilation typically increases and the decision to proceed to tracheostomy with long-term invasive ventilation becomes an individual choice for the family of the child (van der Pol et al. 2013). Ideally the palliative care team should meet the family soon after diagnosis to help them understand the difference between prolonging life and improving quality of life in accordance with the severity of the condition of the child and family choice for intervention at every step of the management.

Decreased feeding followed by failure to thrive is often the first manifestation of progressive weakness and in a vicious circle poorly nourished children become fatigued and more susceptible to respiratory infections: early gastrostomy is often recommended to improve the quality of life.

It has been reported in the literature that some patients with SMA type 1 can have heart defects, mostly atrial and ventricular septal defects as well as possible involvement of the autonomic system which might cause arrhythmia and sudden death (Rudnik-Schoneborn et al. 2008; Shababi et al. 2010).

A large retrospective study of long-term ventilated SMA type 1 patients demonstrated that 15 of 63 patients experienced severe, symptomatic bradycardia (Bach et al. 2007) while a series of autonomic tests on SMA type 1 patients revealed a sympathetic-vagal imbalance, fluctuation of blood pressure and irregular skin responses to temperature changes (Hachiya et al. 2005). Additionally, vascular abnormalities such as distal digit necrosis have been occasionally reported in SMA type 1 patients, also associated with atrial septal defect and asymmetrical left ventricular hypertrophy (Araujo et al. 2009; Rudnik-Schoneborn et al. 2010) while other studies have also highlighted brain involvement, with thalamic lesions (Ito et al. 2004) and sensory nerve involvement (Rudnik-Schoneborn et al. 2003).

While the muscle weakness that dominates the clinical presentation of SMA type 1 clearly plays the largest role in determining the condition morbidity, the full contribution of other organs to the disease manifestation and progression is still a matter of debate both in the human and in animal models.

<table>
<thead>
<tr>
<th>SMA type</th>
<th>Age at onset</th>
<th>Maximum function</th>
<th>Prognosis</th>
<th>Proposed classification</th>
<th>SMN2 copy no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 (very severe)</td>
<td>Neonatal with prenatal signs</td>
<td>Never sits</td>
<td>If untreated no survival beyond first months after birth</td>
<td>1a, head control never achieved, symptomatic in neonatal period; 1b, head control never achieved, onset after neonatal period</td>
<td>One or two copies of SMN2 in 80% of patients</td>
</tr>
<tr>
<td>Type 1 (severe)</td>
<td>0–6 months</td>
<td>Never sits</td>
<td>If untreated life expectancy &lt;2 years</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Type 2 (intermediate)</td>
<td>7–18 months</td>
<td>Sits but never stands</td>
<td>Survival into adulthood expected</td>
<td>Decimal classification according to functional level from 2.1 to 2.9</td>
<td>Three copies of SMN2 in &gt;80% of patients</td>
</tr>
<tr>
<td>Type 3 (mild)</td>
<td>&gt;18 months</td>
<td>Stands and walks</td>
<td>Normal life expectancy</td>
<td>3a, onset of weakness before 3 years; 3b onset of weakness after 3 years</td>
<td>Three or four copies of SMN2 in 96% of patients</td>
</tr>
<tr>
<td>Type 4 (adult)</td>
<td>10–30 years</td>
<td>Stands and walks</td>
<td>Normal life expectancy</td>
<td>–</td>
<td>Four or more copies of SMN2</td>
</tr>
</tbody>
</table>

### Table 24.1 Classification of chromosome 5 spinal muscular atrophy

<table>
<thead>
<tr>
<th>SMA type</th>
<th>Age at onset</th>
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<th>Prognosis</th>
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<td>Stands and walks</td>
<td>Normal life expectancy</td>
<td>–</td>
<td>Four or more copies of SMN2</td>
</tr>
</tbody>
</table>
Recently decreased vascular density was reported in skeletal muscle of both the SMA mouse model and in children with SMA type 1 (Somers et al. 2016).

**SMA TYPE 2 (INTERMEDIATE, sometimes referred to as DUBOWITZ DISEASE)**

Patients with SMA type 2 usually present between the age of 7 and 18 months as they acquire the ability to sit unsupported but are unable to walk. Some of these children may benefit from support of assistive devices for standing and even walking.

These patients have marked proximal weakness affecting the lower limbs more than the upper limbs, muscle hypotonia and areflexia. An almost invariable complication due to the axial muscle weakness is progressive scoliosis with increasing pelvic obliquity and seating instability that in combination with intercostal weakness leads to reduced lung function (Fujak et al. 2005, 2007, 2010a, 2010b, 2011). These children also develop contractures in the lower and upper extremities while very often a subtle hand tremor and increase in palm sweating are present, which can aid in diagnosing the condition.

Cognitive function is well preserved and the overall experience in clinical practice is that infants with SMA type 2 have an early speech development in comparison to their normally developing peers (von Gontard et al. 2002).

The progress can vary greatly and life expectancy is somewhat reduced as a result of the risk of respiratory compromise (Zerres and Rudnik-Schoneborn 1995; Crawford 2003) but most SMA type 2 patients live well into adulthood and a study published in 1997 on 240 Type 2 patients reported a survival rate of 95% at 5 years and 68.5% at 25 years (Zerres et al. 1997).

Respiratory complications in type 2 patients are less severe than in type 1. For the respiratory assessment physical examination and assessment of cough effectiveness with respiratory muscle function tests should be routinely undertaken as indicated in the standard of care guidelines (Somers et al. 2016). Forced vital capacity should be measured in children older than 5 years while in younger patients regular sleep studies can be offered. Overnight oximetry should be regularly undertaken, especially in patients with severely reduced vital capacity (<65% predicted) or with clinical signs of nocturnal hypoventilation that should be treated with non-invasive ventilation (Markstrom et al. 2010).

**SMA TYPE 3 (MILD OR KUGELBERG-WELANDER DISEASE)**

Patients with SMA type 3 are able to stand alone and walk at some point of their motor development. Symptoms of muscle weakness usually appear after 18 months of age but this is very variable and sometimes symptoms may not appear until late childhood. From a clinical standpoint these children have progressive symmetrical and proximal weakness affecting the legs more than the arms and can present with hand tremor.

SMA type 3 is subdivided into SMA type 3a with disease onset before three years of age and the milder form SMA type 3b with an onset after the age of 3 years. Patients with SMA type 3 have a normal life expectancy (Munsat and Davies 1992; Zerres and Rudnik-Schoneborn 1995).

While by definition all these patients acquire independent ambulation, there is often progression of difficulties and patients with SMA type 3a often lose the ability to walk, typically during major growth spurts such as puberty: it has been reported that about half of patients with SMA type 3 will lose independent ambulation by age 14 years (Russman et al. 1996; Rudnik-Schoneborn et al. 2001). These patients then need wheelchairs and may develop scoliosis, obesity and other complications related to lack of mobility (D’Amico et al. 2011; Kaufmann et al. 2012).

**SMA TYPE 4 (ADULT-ONSET)**

SMA type 4 is a less common form that begins in adulthood (>18 years) with symptoms that are usually mild to moderate and include proximal muscle weakness, difficulty walking, muscle tremor and twitching; life expectancy is not affected (Zerres and Rudnik-Schoneborn 1995). This group includes patients able to walk in adulthood and without respiratory and nutritional problems.

**GENETICS OF 5-PROXIMAL SMAs**

SMA is one of the most common genetic disorders with an incidence of one in 6000–11000 live births and a carrier frequency of about one out of 50 (estimated at from 1:38 to 1:70 depending on ethnic group) (Pearn 1978; Ogino et al. 2002, 2004; Sugarman et al. 2012). SMA is inherited as an autosomal recessive condition and in particular by the homozygous mutations of the SMN1 gene. The diagnostic test demonstrates the homozygous deletion of the SMN1 gene in most patients and has 95% sensitivity and nearly 100% specificity (Somers et al. 2016). If copy number analysis suggests the patient carries one intact copy of SMN1 the coding region of the undeleted allele should be sequenced to assess the presence of a second causative mutation, usually subtle sequence variations such as point mutations, small insertions or deletions, or splice site mutations. Sequence analysis of SMN1 is recommended for patients with two copies of SMN1 who have typical symptoms and who are born to consanguineous parents or originate from genetic isolates as homozygosity for minor point mutations in SMN1 have been rarely reported (Cusco et al. 2003).

A large inverted duplication region located at chromosome 5q have caused two forms of the SMN gene exist on each allele.
in humans: a telomeric form (SMN1) and a centromeric form (SMN2). The coding sequence of SMN2 differs from that of SMN1 by a single nucleotide (840C > T) which does not alter the amino acid sequence but results in alternative splicing of exon 7. The alternative splicing of exon 7 causes SMN2 genes to produce a small amount of full-length transcripts (SMN-H) and protein while most of the transcript lacks exon 7 which give rise to a truncated and unstable protein (Vitte et al. 2007). The small proportion of full-length transcript derived from SMN2 provides a sufficient amount of SMN protein to prevent lethality yet not enough to fully compensate for the loss of SMN1, resulting in motor neuron disease. Importantly, the intrinsic instability of the 5q chromosomal duplication can cause multiple copies of SMN2 to be present in different individuals and a higher SMN2 copy number correlates inversely with disease severity (McAndrew et al. 1997; Wirth et al. 2006): all patients retain at least one copy of SMN2, generally two to four. Less than 10% of patients with SMA type 1 retain only one copy of the SMN2 gene and generally have a congenital onset as well as very severe and early lethal course (also sometimes denoted as SMA type 0) (Mercuri et al. 2012) (Table 24.1).

The majority (80%) of patients with SMA type 1 have two copies of SMN2 (Gavrilov et al. 1998) while three SMN2 copies present in more than 80% SMA type 2, with three to four copies identified in 95% of SMA type 3: patients with the adult form typically carry four or more copies of SMN2 (Table 24.1) (Feldkotter et al. 2002; Rudnik-Schoneborn et al. 2009). SMN genes encode for a protein ubiquitously expressed and localised in the cytoplasm and in the nucleus, particularly abundant in motor neurons of the spinal cord (Rudnik-Schoneborn et al. 2009). Within the nucleus SMN protein is concentrated in dot-like structures associated with coiled (Cajal) bodies, named ‘gems’ (gemini of coiled bodies). Although the exact cellular function of SMN protein responsible for the pathogenesis of SMA remains unknown, cells from patients with SMA contain fewer gems compared with controls and carriers (Liu and Dreyfuss 1996).

Several animal models have been obtained in yeast, nematode, fly, zebrafish and mouse by disruption of SMN expression. These SMA models have been fundamental for increasing knowledge about the molecular and cellular pathways of SMN but also allowed investigators to better understand the mechanism(s) of disease and provide a platform from which high-throughput genetic and drug screenings have been performed (Schmid and DiDonato 2007). To explain the pathogenesis of SMA two main hypotheses have been postulated (D’Amico et al. 2011): (1) SMN is involved in the biogenesis of small nuclear ribonucleoproteins (snRNPs) and in mRNA splicing; thus SMN reduction may affect snRNP assembly (to which motor neurons may be more sensitive) and/or SMN complex is involved in the splicing of one or few transcripts with a key function in motor neurons. (2) SMN also appears to have a motor neuron specific function such as mRNA transport along the axon so that transcription can occur close to the nerve terminal endings. Although SMN protein is expressed in all somatic cells it is unclear why motor neurons of the spinal cord are specifically vulnerable in SMA. In support of hypothesis 1 some studies suggest SMN protein might play a key role in cellular functions unique to motor neurons (Carvalho et al. 1999; Fan and Simard 2002; Gabanella et al. 2007). In support of the second hypothesis, other studies suggest SMN protein might sustain the survival of motor neurons by allowing normal axonal transport and maintaining the integrity of neuromuscular junctions.

In addition to the above hypothesis it has been recently demonstrated that SMN is required for 3-end formation of histone mRNAs. Defective 3′-end processing can lead to a reduction in the mRNA and protein levels of replication-dependent histones meaning that the consequences of SMN deficiency are largely related to the disruption of fundamental RNA processing, relevant both for neurons and other cell types outside the nervous system (Hamilton and Gillingwater 2013).

There is a better correlation between the level of SMN protein and severity of disease compared to the simple assessment of the SMN2 copy number, suggesting that not all SMN2 genes are transcribed with the same efficiency (Sumner et al. 2006). Usually, SMA-affected siblings are very similar in terms of their age at onset and the progression of disease (Rudnik-Schoneborn et al. 1994) but there can be discordance of phenotype severity in siblings carrying identical numbers of SMN2 genes, suggesting the influence of modifier genes (Cobben et al. 1995; Hahnen et al. 1995; Wång et al. 1996; Prior et al. 2004). In the last decade SMA-discordant families with asymptomatic females who had inherited the same SMN1 and SMN2 alleles as their affected siblings were reported (Hahnen et al. 1995; Oprea et al. 2008) and it was suggested that unaffected SMN1-deleted females have significantly higher expression of plastin 3 (PLS3) than their SMA-affected counterparts. PLS3, a protein important for axonogenesis, has been suggested to be an SMA disease modifier (Oprea et al. 2008); however, this role remains uncertain as no changes in the PLS3 gene have been reported so far.

**KEY DIAGNOSTIC FEATURES AND DIFFERENTIAL DIAGNOSIS**

Clinical features are highly suggestive for the diagnosis of SMA particularly in the severe variant of a floppy infant or weak child. The facial expression and attentiveness are typically good with the weakness usually symmetrical and more proximal than distal, affecting the legs more than the arms.

The clinical differential diagnosis with SMA type 1 should include the congenital myopathies or central nervous system (CNS) pathologies leading to profound hypotonia. However, the typical pattern of preserved diaphragmatic breathing together with preserved facial expression and the lack of tendon reflexes would guide the diagnosis. Similarly, in SMA...
Chapter 24 Diseases of the Motor Neuron

The tests below have been used in the past to establish the diagnosis of SMA but currently have little or no role in the diagnosis of most affected individuals. They are used primarily if molecular genetic testing of SMN1 does not identify mutations.

**Muscle histology** Muscle biopsy reveals group atrophy of type 1 and type 2 muscle fibres as opposed to the normal checkerboard pattern. Rare angulated and large type 1 fibres are scattered throughout. Muscle biopsy findings can sometimes help to establish the diagnosis but they do not help predict the severity of disease among infants with this condition (Buchthal and Olsen 1970; Zalneraitis et al. 1991). With the advent of rapid genetic screening the role of a muscle biopsy is now not recommended.

**Nerve histology** This is not a recommended diagnostic test for SMA. Hypomyelination of the peripheral nerve can nevertheless be observed in the severe type 0 form otherwise the sensory nerves (conventionally biopsied) usually show normal histology, meaning that this technique should not be used for the diagnosis of SMA (Korinthenberg et al. 1997; MacLeod et al. 1999; Hergersberg et al. 2000).

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**Table 24.2 Most common differential diagnosis of infantile/childhood 5q-spinal muscular atrophy (SMA)**

<table>
<thead>
<tr>
<th>SMA type</th>
<th>Other Motor Neuron Disorders</th>
<th>Myopathies/Dystrophies</th>
<th>Neuropathies</th>
<th>Neuromuscular Junction Disorders</th>
<th>Other Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA 1</td>
<td>SMARD1 BVVL FLD Juvenile SMA Other rare non-5q-SMA</td>
<td>Congenital myopathies Metabolic myopathies (Pompe) Mitochondrial myopathies Congenital myotonic dystrophy Congenital muscular dystrophies</td>
<td>Congenital hypomyelinating or axonal HMSN</td>
<td>Congenital myasthenic syndrome Botulism</td>
<td>CNS abnormality Chromosomal abnormality Spinal cord disorders</td>
</tr>
<tr>
<td>SMA 2</td>
<td>BVVLS &amp; FLD Juvenile SMA Other rare non-5q-SMA</td>
<td>Congenital myopathies Congenital muscular dystrophies Metabolic myopathies (Pompe) Mitochondrial myopathies</td>
<td>Congenital hypomyelinating or axonal HMSN CIDP</td>
<td>Congenital myasthenic syndrome Autoimmune myasthenia gravis</td>
<td>CNS abnormality Chromosomal abnormality Spinal cord disorders</td>
</tr>
<tr>
<td>SMA 3</td>
<td>Juvenile SMA Other rare non-5q-SMA</td>
<td>Congenital myopathies Congenital muscular dystrophies (DMD/BMD/LGMD) Metabolic myopathies (Pompe) Mitochondrial myopathies Inflammatory myopathies Channelopathies</td>
<td>Axonal HMSN CIDP</td>
<td>Congenital myasthenic syndrome Autoimmune myasthenia gravis Lambert-Eaton myasthenic syndrome</td>
<td>CNS abnormality Chromosomal abnormality Spinal cord disorders</td>
</tr>
</tbody>
</table>

**Electromyography** Electromyography (EMG) reveals denervation and diminished motor action potential amplitude. The EMG regular spontaneous motor unit activity, a unique feature in SMA, is seen most commonly in SMA type 1 and occasionally type 2, but not in type 3 (Hausmanowa-Petrusewicz and Karwanska 1986; Shababi et al. 2010). A reduced interference pattern is seen with maximal effort with polyphasic waves, positive sharp waves and fibrillations present in all individuals with SMA, while motor and sensory nerve conduction velocities (NCVs) are normal. This test remains a useful tool in the diagnosis of SMA.

Trembling of the baseline trace on a standard ECG can already give the first clue of denervation due to intercostal muscles denervation. The first-level diagnostic test for a patient suspected to have SMA should be the search of the SMN1 gene for homozygous deletions. The absence of SMN1 exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMA (Somers et al. 2016) while if first-level assay tests are negative further laboratory examinations including creatine kinase levels, which can be mildly elevated especially in type 3 patients (Rudnik-Schoneborn et al. 1998), and electrophysiological tests such as electromyography (EMG) and nerve conduction study should be performed. If EMG suggests a motor neuron disorder (Hausmanowa-Petrusewicz and Karwanska 1986) then further testing for SMN mutations should be pursued with the techniques mentioned above.

---

STANDARD OF CARE IN SMA

There have been recent meetings and consensus guidelines for aspects of diagnosis, assessment and monitoring of SMA published in 2007 (Somers et al. 2016). Clearly there have been remarkable improvements in the outcome of patients with SMA in the last decade. However, complete agreement on systematic management in several areas is still lacking, although it is clear that patients with SMA and their families should be supported by a multidisciplinary team (Roper and Quinlivan 2010). In this chapter we will concentrate the discussion on the following aspects: respiratory, feeding/nutrition and orthopaedic issues.

Respiratory

Patients with SMA type 1 are the most fragile group and respiratory muscle weakness is an inevitable feature, with early intercostal weakness being particularly prominent. Infants should be examined regularly to review cough effectiveness, work of breathing and presence of paradoxical (diaphragmatic) breathing and evolution of chest deformity. Assessment of efficacy and safety of swallow should be undertaken by a speech and language therapist to reduce the risk of aspiration. In order to prevent infections infants should receive all standard immunisations. Clinical experience suggesting that physiotherapy helps with secretion clearance in infants with severe SMA type 1. Intermittent chest percussion, appropriate positioning and nasopharyngeal suctioning may provide benefit to parents and children can be taught these techniques by a paediatric physiotherapist experienced in respiratory management. The use of a mechanical insufflator/exsufflator via a face mask (cough assist machine) increases peak cough flow and aids airway clearance, with such devices having been demonstrated as effective in reducing infection in older children with neuromuscular conditions. As some degree of patient cooperation is essential for success, their use in very young infants is challenging. However, those experienced in their use find that cough assist devices may be used in infants from 6 months of age (Chatwin et al. 2003; Miske et al. 2004; Vianello et al. 2005; Fauroux et al. 2008).

An early discussion should include the option of noninvasive ventilation and secretion management because of the rapid progression of the disease while anticipatory guidance and education for chronic care, illness management and perioperative care should also be provided (Somers et al. 2016). The natural history of SMA1 has changed substantially in the past decade because of the availability of new technology and implementation of an aggressive approach to improve survival and quality of life (Schroth 2009). Noninvasive ventilation (NIV) can be used at a very young age—as early as the neonatal period—because interfaces are now available for small infants (Simonds 2007) while bilevel positive airway pressure ventilation can be provided at home with a face mask, with evidence suggesting NIV may reduce the frequency of hospital admissions (Rudnik-Schoneborn et al. 2008). The use of NIV can also have a beneficial impact on chest shape, reducing the development of the typical chest deformities that characterises SMA type 1 (Bach and Bianchi 2003).

As weakness progresses the requirement for ventilation might increase to 24 hours per day. With full-time ventilation the upper airway can become damaged, resulting in oedema and increased secretions and such complications in the airway or intercurrent infections can necessitate intubation.

Whether to proceed to tracheostomy for long-term invasive ventilation is an individual choice for the family of the child and the involvement of the palliative care team to offer support and advice to families who have to make difficult decisions is recommended. Children with SMA type 1 who undergo tracheostomy and long-term ventilation remain dependent on ventilators for the rest of their lives: speech develops in infants treated with NIV but development is more challenging in those ventilated by tracheostomy (Bach et al. 2007), with some patients at high risk of recurrent hypoxia, which results in ischaemic brain injury. The goal of intervention should always be to improve quality of life of the child, not to prolong life (Roper and Quinlivan 2010).

Patients with SMA type 2 also have weak intercostal muscles and invariable scoliosis contributes to progressive restrictive lung disease (Iannaccone 2007; Schroth 2009) that can result in onset of sleep disordered breathing: regular sleep studies are recommended. Initiation of NIV in children with abnormal respiratory studies typically leads to improvement in their symptoms (fatigue, headaches, disturbed sleep and lack of appetite in the morning) (Mellies et al. 2004).

Feeding and Nutrition

In infants with SMA type 1 the suck is invariably weak, feeding inefficient and growth possibly compromised. With progressive bulbar and respiratory involvement there is an increased risk of aspiration of liquids, solid food and saliva as the poor head control exacerbates swallowing difficulties leading to silent aspiration and eventually respiratory tract infections. Infants’ feeding and swallowing should be assessed by a speech and language therapist who can offer advice on safe swallow: a videofluoroscopy can objectively assess the swallow and demonstrate silent aspiration in case of doubt. These infants are also at risk of developing gastro-oesophageal reflux so should be assessed for symptoms to be managed appropriately. As oral feeds alone are usually not sufficient to sustain growth supplementation using nasogastric feeding or a gastrostomy should be considered early in the course of the disease before significant failure to thrive occurs. The volume of feed depends on the energy of the infant and their protein requirements: there are various equations available to calculate energy expenditure but none has been validated for infants with type 1 SMA (Roper and Quinlivan 2010).

Feeding and swallowing difficulties are not uncommon in SMA type 2 but rare in type 3, while gastro-oesophageal reflux can be present also in this population. Growth failure can occur for various reasons, from reduced intake because of masticatory muscle fatigue or prolonged meal times to recurrent...
respiratory infections. Development of dysphagia due to progressive weakness of bulbar and oesophageal muscles can occur in adolescents with SMA type 2 (Chen et al. 2012) while restriction of movements of the temporomandibular joint is also present in some individuals. At the other extreme reduced activity and low energy expenditure increases the risk of obesity but little evidence exists about how best to monitor these patients (Sproule et al. 2009, 2010a, b).

Orthopaedic

Children with SMA type 1 are almost invariably too severely affected to be eligible for orthopaedic surgical interventions but supported seating and passive stretching may be useful. Scoliosis occurs in almost all non-ambulant patients which can be controlled by spinal braces, other sitting adjustments or trunk orthoses (Granata et al. 1989; Tangsrud et al. 2001). Growing rods (Akbarnia et al. 2005) or vertical expandable prosthetic titanium ribs (Emans et al. 2005; Hell et al. 2005) can also be used to prevent progression of scoliosis in very young children if bracing is unsuccessful: such techniques have been effective in controlling progressive early-onset scoliosis before definitive spinal fusion (Thompson et al. 2007; Chandran et al. 2011; McElroy et al. 2011).

Newborn Screening for SMA

In the past decade development and implementation of standard of care protocols and proactive approach have improved survival in children with SMA types 1 and 2. At the same time exciting novel therapies are at various stages of development with some having recently successfully completed randomised clinical trials. For therapy to be as effective as possible it is necessary for it to be administered as close as possible to the onset of clinical symptoms and ideally ahead of the development of such as this imply loss of motor neurons, which is likely to be an irreversible phenomenon.

As an example, in SMA type 1 the pathological process typically begins in the perinatal period with loss of more than 90% of motor units within 6 months of age. Swoboda et al. performed a prospective study in prenatally diagnosed infants with SMA type 1, showing that in association with the initial onset of symptoms or decline in function there was electrophysiological evidence of abrupt denervation (Swoboda et al. 2005). With this fast rate of neuronal loss, the extent of therapeutic response in infants with SMA type 1 is likely to be influenced by the timing of the intervention and this has been very clearly demonstrated in the preclinical models of the disease. The benefit of novel therapeutics should therefore ideally be assessed as close as possible to the birth and presymptomatic diagnosis. The purpose of newborn screening would be, therefore, not only to provide genetic counselling to families as early as possible in order to avoid the birth of more affected children in a family but, with the advent of experimental therapies in which early data appears to be extremely encouraging, also to identify affected infants prior to the presentation of clinical symptoms. Studies have been conducted to examine the legal, ethical and social issues with population-based pilot studies for SMA (Rothwell et al. 2013; Wood et al. 2014).

In 2008 SMA was submitted for formal consideration to the US Health and Human Services Secretary’s Advisory Committee on Heritable Diseases in Newborns and Children by a collaborative group of physicians, researchers, the SMA community and the families of SMA. The consensus of the internal Nomination and Prioritization Workgroup of the committee was that the addition of SMA to the uniform screening panel was premature at that time (for more information visit http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/). Since then clinical trials have made considerable progress and the validation of screening methods in public health by newborn blood spot screening laboratories is now underway (Pyatt and Prior 2006; Pyatt et al. 2007; Prior 2010; Prior et al. 2010; Dobrowolski et al. 2012; Taylor et al. 2015). An initial pilot has been completed by the Wadsworth Center of the New York State Department of Health with further validation planned and a population-based pilot study in Taiwan that began in November 2014 had detected two children affected within 4 months (Han 2015).

Approved and experimental therapies aiming at increasing SMN protein levels

With Greater understanding of the molecular basis of SMA in the past two decades a major focus of therapeutic developments has been on increasing the full-length SMN protein by enhancing SMN2 gene expression, increasing the inclusion of exon 7 in SMN2 transcripts, stabilising the SMN protein or replacing the SMN1 gene (for more information visit: SMA Drug Pipeline <http://www.curesma.org/research/latest-advances/>). Within few months, the treatment scenario for SMA has dramatically changed as an oligonucleotide drug, called Spinraza, has received FDA approval for the treatment of SMA in the US in December 2016 and more recently EMA approval in Europe (April 2017).

Ongoing clinical trials include (1) antisense oligonucleotides, (2) small-molecule drugs, and (3) gene therapy.

(1) Antisense oligonucleotides (ASO) Splice switching ASO are synthetic RNA molecules that interfere with physiological splicing of exons. As all patients with SMA carry at least one copy of SMN2, in which a single nucleotide change determines an exclusion of exon 7 in 90% of the transcript, an attractive approach is to manipulate SMN2 splicing so that exon 7 is retained in the mature transcript, so as to create a mRNA and eventually a protein identical to the one produced by SMN1. These ASOs are highly effective at promoting inclusion of exon 7 in SMN2 transcripts and increasing SMN
protein levels both in vitro and in vivo, although they are not capable of crossing the blood–brain barrier so require intrathecal administration (Hu et al. 2011; Forenisky et al. 2012).

Following the positive results of the interim analysis in a large randomised double blind controlled clinical trial (ENDEAR) in which infants under 7 months of age with SMA type 1 received either Spinraza or sham procedure (control arm), this study was interrupted and all participants offered to enter an open label phase (called SHINE). After interrupting the study Spinraza have received FDA approval and is currently licensed in US for patients with SMA. The pharmaceutical sponsor, Biogen, has offered to the trial sites in several European countries, the possibility to enroll more patients with SMA type 1 via an Expanded Access Program (EAP) which is currently ongoing (for more information visit www.biogen.com).

(2) Small molecules A number of low-molecular-weight drugs can modestly increase levels of full-length SMN protein by activating the SMN2 promoter, increasing expression, or altering the splicing pattern of SMN2 transcripts so as to favour the inclusion of exon 7 (Tsai et al. 2008; Hastings et al. 2009).

Histone deacetylase inhibitor and quinazoline compounds increase SMN2 mRNA levels and improve the disease phenotype in mouse models of SMA (Avila et al. 2007; Narver et al. 2008; Garbes et al. 2009; Riessland et al. 2010).

Other small-molecule drugs such as aminoglycosides promote reading of the stop codon of SMNΔ7 transcripts, enabling the translation of a protein variant with, however, increased stability when compared to the SMN2 product (Mattis et al. 2009). These molecules had shown promising results in mouse models and cell lines derived from patients with SMA but when tested in clinical trials showed little or no benefit (Mercuri et al. 2007; Oskoui and Kaufmann 2008; Swoboda et al. 2009).

Another small-molecules member – quinazoline – increases full-length mRNA by inclusion of exon 7 in SMN2 gene transcript, resulting in an increase in SMN protein levels. The primary function is in the inhibition of human scavenger decapping enzyme (DcPS). The role of DcPS is best understood in the degradation of the 5’ cap during the 30–50mRNA decay and may have additional functions in nuclear–cytoplasm transportation as well as first intron pre-mRNA splicing (Shen et al. 2008). Quinazoline is anticipated to progress to phase I clinical trials.

RG7800 is a small molecule SMN2 splicing modifier being developed by Roche for the treatment of SMA. A phase I multicentre randomised, double blind, placebo-controlled study was initiated in 2015. The purpose of the study is to administer multiple doses to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RG7800 following 12 weeks of treatment in adult and paediatric patients with SMA. After recruiting the first cohort of patients the study has suspended participant recruitment due to unexpected eye findings observed in an animal study evaluating the long term safety of RO7800 (study on holding and suspended participant recruitment in April 2015; for more information visit www.clinicaltrials.gov). More recently Roche has initiated another phase I study for SMA 1 and 2/3 with a related compound: Novartis is also pursuing a similar strategy with a small molecule also capable of increasing exon 7 retention in SMN2 gene, in SMA1 (https://clinicaltrials.gov/ct2/show/NCT02268552).

(3) Gene therapy As a monogenic disease SMA is a good target for vector-based gene replacement therapy to restore a normal form of the SMN1 gene in patients. Viral-mediated SMN gene delivery has been remarkably successful in preclinical studies. Both systemic and intra-cerebro-ventricular injection of self-complementary adeno-associated viral vectors (scAAV) expressing SMN showed efficient transduction of motor neurons in both mice and nonhuman primates as well as nearly complete correction of the SMA phenotype in mice (Foust et al. 2010; Passini et al. 2010; Valori et al. 2010).

In selecting a potential vector to deliver the SMN1 gene adeno-associated virus vectors (AAV) 8 and 9 appeared to be excellent contenders as a result of their ability to cross the blood–brain barrier through the vascular system in mouse models (Valori et al. 2010; Dayton et al. 2012; Seo et al. 2013).

At the time of writing, AveXis is conducting the first gene therapy phase I clinical trial to assess the safety of multidose intravenous delivery of scAAV9-SMN in infants with SMA type 1 at Columbus University in the United States (for more information visit www.clinicaltrials.gov).

OTHER THERAPEUTIC APPROACHES

Neuroprotective compounds Olesoxime is another small molecule that has showed neuroprotective properties in a number of in-vitro and in-vivo studies promoting neurite outgrowth and communication with the mitochondrial permeability transition pore (Bordet et al. 2007).

This compound has been tested in a phase II randomised, multicentre, double blind, placebo-controlled trial completed in 2013. A total of 165 nonambulant patients with SMA types 2 and 3, aged 3–25 years, were recruited in 23 sites in different European countries (France, Germany, Italy, United Kingdom, Poland, Netherlands, Belgium) and followed in the study for approximately 2 years. The randomisation ratio was 2:1, therefore 108 in the olesoxime group (10mg/kg) and 57 in the placebo group with preliminary results suggesting olesoxime maintains motor function and improves overall health status over the 2-year treatment period.

An open-label study to evaluate long term safety, tolerability and effectiveness of olesoxime in patients with
SMA has recently started recruiting patients who participated in the phase II study (for more information visit www.clinicaltrials.gov).

**ALBUTEROL**

Albuterol is a beta-adrenergic agonist recognised to have a positive anabolic effect in healthy individuals, evaluated in a pilot study on patients with SMA types 2 and 3 that showed a significant improvement of myometry, forced vital capacity and DXA scores at 6 months evaluation (Kinali et al. 2002). A following open label pilot study using salbutamol, a form of albuterol, showed an improvement of the functional scores at the Hammersmith Functional Motor Scale (HFMS) after 6 and 12 months of treatment (Pane et al. 2008). In-vitro studies have also shown that salbutamol can increase the full length SMN mRNA, SMN protein and gem numbers by promoting the exon 7 inclusion with this effect found to be directly proportional to the SMN2 gene copy number (Angelozzi et al. 2008; Tiziano et al. 2010).

**STEM CELLS**

One of the goals of transplanted stem cells is to support endogenous motor neurons through the delivery of neuroprotective agents and ideally also partially restore neuronal and non-neuronal cells (Hedlund et al. 2007; Koliatsos et al. 2008; Suzuki and Svensden 2008). Neural stem cells obtained from the spinal cord administered intrathecally to SMA mice showed appropriate migration into the parenchyma and capability to generate a small proportion of motor neurons: these treated mice exhibited improved motor unit and neuromuscular function and showed a 38% increase in life expectancy (Corti et al. 2008).

Despite the positive results of neural stem cell transplantation in mice translational value in human is unclear and therefore alternative protocols, which include the use of embryonic stem cells or induced pluripotent stem cells for transplantation, have been tried in animal models. These cells have the ability to differentiate in vitro and in vivo into neural stem cells and motor neurons (Wichterle et al. 2002; Li et al. 2005; Dimos et al. 2008).

The findings of improved SMA phenotype in mice following the intrathecal transplantation of embryonic stem cell-derived neural stem cells included proper migration to target tissue in the spinal cord, neuroprotective function and a 58% increase in lifespan (Corti et al. 2010).

A protocol to test neuronal stem cells in patients with SMA is currently on hold by the FDA. However, there are no imminent clinical trials expected in humans (Taylor et al. 2015).

Similarly, a controversial approach of allogenic mesenchymal cell transplantation, administered intravenously and intrathecally, initiated by a private enterprise in Italy, was interrupted in 2014 by a panel of experts appointed by the Italian Ministry of Health. Concerns cited included a lack of proven efficacy and serious concerns on the quality of the proposed drug as the mesenchymal cells given to patients were not grown under the approved EU strict set of quality control standards.

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**NON-5q SPINAL MUSCULAR ATROPHIES**

There are other inherited motor neuron disorders not caused by mutation of the SMN gene (non-5q spinal muscular atrophy) that present with early denervation weakness but different clinical symptoms from those of the common 5q variant (Zerres and Rudnik-Schoneborn 2003). These disorders can be classified on the basis of the clinical distribution of weakness and the pattern of inheritance (Table 24.3).

**CONGENITAL DISTAL VARIANTS OF SMAS, MOST OFTEN AFFECTING THE LOWER LIMBS (SMA-LED)**

Autosomal dominant congenital SMA-LED, also known as congenital spinal muscular atrophy affecting predominantly the lower limbs, or ‘distal SMA’, has been clinically described for decades and is characterised by congenital or early childhood onset, motor neuron degeneration confirmed on electromyography and lower limb–predominant weakness (Fleury and Hageman 1985; Frijns et al. 1994; van der Vleuten et al. 1998; Mercuri et al. 2004).


These SMA-LED variants share core phenotypic features including congenital/early childhood onset, very slow progression or more frequently static course and lower limb–predominant weakness; however, there are also some distinctive features.

Dominant mutations in TRPV4 have been described in both peripheral nervous system and skeletal diseases. The peripheral nervous system diseases include hereditary motor and sensory neuropathy type 2C or Charcot–Marie–Tooth disease type 2C (HMSN2C or CMT2C), congenital spinal muscular atrophy and arthrogryposis (CSMAA) as well as scapuloperoneal spinal muscular atrophy (SPSMA). Vocal cord paralysis and sensorineural hearing deficit are frequently associated findings in patients with neuropathies. Muscle MRI of the thighs and calf muscles from some patients with SMA associated with TRPV4 mutations demonstrate a selective...
<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Gene/locus</th>
<th>Phenotype, characteristic clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal SMA +/- distal involvement</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SMA with late onset (Finkel disease)</td>
<td>AD</td>
<td>VAPB</td>
<td>Proximal weakness that begins in lower limbs and then progresses to upper limbs, onset after third decade and benign course. Most of the patients remain ambulatory 10 to 40 years after clinical onset.</td>
</tr>
<tr>
<td>SMA-LED CMT2 Scapuloperoneal SMA</td>
<td>AD</td>
<td>TRPV4</td>
<td>Congenital and non-progressive with lower limb predominance, vocal cord paralysis</td>
</tr>
<tr>
<td>SMA-LED</td>
<td>AD</td>
<td>DYNC1H1</td>
<td>Congenital, non-progressive, contractures, lower-limb predominant, variable cortical migration defects, learning difficulties</td>
</tr>
<tr>
<td>SMA-LED +/- hereditary spastic paraplegia</td>
<td>AD</td>
<td>BICD2</td>
<td>Congenital, contractures, lower-limb predominant, variable pyramidal signs</td>
</tr>
<tr>
<td><strong>Distal SMA/distal hereditary motor neuropathies/neuropathies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMARD1/ HMN6/ DSM1</td>
<td>AR</td>
<td>IGHMBP2</td>
<td>Irreversible diaphragmatic palsy and progressive distal symmetrical muscular weakness (mainly of the lower limb)</td>
</tr>
<tr>
<td>HMN2A</td>
<td>AD</td>
<td>HSPB8</td>
<td>Distal adult type</td>
</tr>
<tr>
<td>HMN2B</td>
<td>AD</td>
<td>HSPB1</td>
<td>Onset from the teenage years through mid-adulthood. Initial symptoms are cramps or weakness in the feet muscles followed by gradual lower leg atrophy</td>
</tr>
<tr>
<td>HMN2C</td>
<td>AD</td>
<td>HSPB3</td>
<td>Onset with weakness and wasting of distal muscles of the anterior tibial and peroneal compartments of the legs. Weakness and atrophy may later expand to the proximal muscles of the lower limbs and/or to the distal upper limbs</td>
</tr>
<tr>
<td>HMN5A</td>
<td>AD</td>
<td>GARS</td>
<td>Distal SMA with upper-limb predominance</td>
</tr>
<tr>
<td>CMT 2D</td>
<td>AD</td>
<td>GARS</td>
<td>Mixed phenotype: some patients have sensorimotor neuropathies while others have only motor symptoms.</td>
</tr>
<tr>
<td>HMN5B</td>
<td>AD</td>
<td>BSCL2</td>
<td>Distal SMA with upper-limb predominance</td>
</tr>
<tr>
<td>SPG17</td>
<td>AD</td>
<td>BSCL2</td>
<td>Silver spastic paraplegia syndrome</td>
</tr>
<tr>
<td>HMN7B</td>
<td>AD</td>
<td>DCTN1</td>
<td>Distal HMN with vocal cord paralysis</td>
</tr>
<tr>
<td><strong>Other rare non-5q spinal muscular atrophies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVVLS</td>
<td>AR</td>
<td>SLC52A1, SLC52A2, SLC52A3</td>
<td>Pontobulbar palsy associated with bilateral sensorineural hearing loss. Common presenting symptom: ataxic gait</td>
</tr>
<tr>
<td>SBMA (Kennedy disease)/ SMAX1</td>
<td>X-linked recessive</td>
<td>androgen receptor (AR)</td>
<td>Onset from adolescence onwards, Spinal and bulbar muscular atrophy, Muscle cramps and progressive weakness</td>
</tr>
<tr>
<td>SMAX2</td>
<td>X-linked recessive</td>
<td>UBA1</td>
<td>Polyhydramnios and poor movements in utero, congenital arthrogryposis, lethal disease, severe hypotonia and areflexia</td>
</tr>
<tr>
<td>JALS</td>
<td>AR</td>
<td>ALS2; SIGMAR1; SPG11; FUS</td>
<td>Onset of disease before 25 years of age; combination of upper and lower motor neuron signs</td>
</tr>
<tr>
<td>SMA-PME</td>
<td>AR</td>
<td>ASAH1</td>
<td>Onset of motor deficits during childhood or at a juvenile age after normal developmental milestones; progressive myoclonic epilepsy</td>
</tr>
<tr>
<td>SMA-PCH</td>
<td>AR</td>
<td>VRK1</td>
<td>SMA with pontocerebellar hypoplasia. Variable age of onset of hypotonia, varying degrees of cerebellar or pontine hypoplasia and atrophy, peripheral nerve involvement, variable survival</td>
</tr>
<tr>
<td>SMA due to mitochondrial dysfunction</td>
<td>AR</td>
<td>SCO2</td>
<td>Mild SMA-like phenotype, possible presentation with stridor and respiratory insufficiency</td>
</tr>
<tr>
<td>Distal SMA</td>
<td>AR</td>
<td>PLEKHG5</td>
<td>Progressive distal muscular atrophy in the legs without clinical sensory loss, later weakness and atrophy may expand to the proximal muscles</td>
</tr>
</tbody>
</table>

SMA-LED, spinal muscular atrophy with lower extremity predominance; CMT, Charcot–Marie–Tooth disease type 2; SMARD1, spinal muscular atrophy with respiratory distress type 1; HMN, hereditary motor neuropathy; DSM1, distal spinal muscular atrophy; SPG, spastic paraplegia; SBMA, spinal-bulbar muscular atrophy; BVVLS, Brown-Vialetto-Van Laere syndrome; SMAX, SMA with X-linked inheritance; JALS, juvenile amyotrophic lateral sclerosis; AD, autosomal dominant; AR, autosomal recessive.
involvement of the vastus medialis, long heads of biceps and semimembranosus as well as of the gastrocnemius (Astrea et al. 2012). A recent study has however described more diffuse fat atrophy at both the thigh and calf level (Evangelista et al. 2015).

Dominant or sporadic missense mutations in the tail domain of the cytoplasmic dynein heavy chain gene 1 (DYNCH1I) were first described by Harms (Harms et al. 2012) as causative of an SMA-LED phenotype although since this first description several individuals have been reported with mutations located in other portions of the gene and also in association with malformations of cortical development (Vissers et al. 2010; Tsurusaki et al. 2012; Fiorillo et al. 2014).

DYNCH1I is a large gene encoding the heavy chain of the cytoplasmic dynein protein complex, a ubiquitously expressed multisubunit molecular motor involved in retrograde axonal transport (Schnapp and Reese 1989), cell migration, nucleokinesis, Golgi localisation and autophagy (Corthesy-Theulaz et al. 1992; Ravikumar et al. 2005; Schiavo et al. 2013).

A compelling candidate mechanism for the pathogenicity of DYNCH1I mutations would be interference with dynein-dependent mitochondrial trafficking leading to mitochondrial dysfunction and subsequent neurodegeneration (Anesti and Scorrano 2006). It has been recently confirmed that mutations in dynein relevant for SMA–LED compromise mitochondrial morphology and function (Eschbach et al. 2013).

We recently reported a large cohort of children and adults affected by SMA-LED due to DYNCH1I mutations which is likely to be the most common subgroup of SMA-LED, expanding the clinical spectrum to include individuals with severe generalised arthrogryposis and instances with onset in adulthood (Fig. 24.1) (Scoto et al. 2015). In this study it was confirmed that in a significant proportion of patients the onset of clinical signs is at birth or in the first few years of life although in approximately one quarter of individuals there were no concerns until adulthood. Almost all individuals acquired the ability to walk irrespective of age at onset and all remained ambulant, confirming the stable course of the disease, with this group of patients showing a more pronounced involvement of the lower limbs in comparison to the upper limbs, with well-preserved muscle function in the arms and only minimal distal (hand) weakness in a few individuals. Despite the clinical appearance of distal muscle wasting and foot deformities the proximal muscles, especially the hip extensors, are the weakest lower limb muscles, in contrast to the more prominent distal weakness reported in dominant SMA families with mutations in TRPV4, suggesting this could be a key clinical aspect in the differential diagnosis. In the majority of individuals contractures are a presenting feature while the muscle MRI of the lower limbs shows a striking pattern, appearing to be highly suggestive of this condition especially at the thigh level with a selective sparing and relative hypertrophy of the adductors compartment and of the semitendinosus muscles (Mercuri et al. 2004; Scoto et al. 2015). It is of interest that this imaging pattern is different from that described in the form of lower-limbs SMA due to mutations in TRPV4 especially at the calf level. (Astrea et al. 2012)

Another feature observed in many individuals is a brain malformation resembling polymicrogyria, characterised by cortical nodularity or gyral overconvolutions, best seen in the frontal and peri-Sylvian cortex with posterior extension of the Sylvian fissures. It has been observed that CNS malformations are often associated with a degree of cognitive impairment and behavioural difficulties resembling attention-deficit-hyperactivity disorder (Scoto et al. 2015).

More recently, mutations in the dynein adaptor protein BICD2 have been identified in a series of patients also characterised by SMA with predominant lower extremity involvement (Neveling et al. 2013; Oates et al., 2013; Peeters et al. 2013; Synofzik et al. 2014). These patients also had lower limbs disproportionately affected with the degree of wasting often out of proportion to the degree of weakness. Mutations in BICD2 typically cause early onset non-length dependent lower limb predominant weakness, wasting and contractures with a relatively static clinical course. The marked degree of lower limb muscle involvement is also evident on muscle MRI which shows a characteristic pattern of muscle fat replacement and selective hypertrophy similar to that seen in patients with DYNCH1I mutations. Despite the lower extremity predominance mild upper limb involvement such as scapular winging can be present in a subset of patients. While the motor phenotype associated with BICD2 mutations is similar to that seen in individuals with DYNCH1I mutations malformations of cortical development have not been reported so far in patients with BICD2 mutations. While the phenotype of early-onset, lower extremity predominant wasting and weakness is common to most patients with mutations in BICD2 there is considerable heterogeneity in terms of the severity of the phenotype, with the reason for phenotypic heterogeneity unknown but having important implications for genetic counselling: in a proportion of patients with BICD2 there is involvement of upper motor neurons as well. The clinical similarity between BICD2- and DYNCH1I-spinal muscular atrophy, lower extremity predominant, has highlighted dynein-dynactin trafficking as a key cellular pathway in motor neuron patterning, primary development and survival (Rossor et al. 2015).

**BROWN-VIALETTA-VAN LAERE SYNDROME AND FAZIO-LONDE DISEASE**

Brown-Vialetto-Van Laere syndrome (BVVLS) (OMIM 211530) is a rare neurological disorder first described by Brown in 1894 and later by Vialetto and Van Laere. It is characterised by progressive ponto-bulbar palsy associated with bilateral sensorineural hearing loss, mainly affecting cranial nerves VII–XII, often with progression to involve the anterior horn cells of the spinal cord over time. The same clinical presentation without deafness is traditionally known as Fazio-Londe Disease (FLD) although the two are now regarded as part of a spectrum of neuronopathic disorders.
Figure 24.1  Clinical phenotype, muscle imaging and brain imaging in different forms of spinal muscular atrophy with lower extremity predominance (SMA-LED)

Images (a)–(d) show SMA-LED caused by mutations in DYNC1H1. (a) Standing with support at 8 years of age and distal wasting in lower limbs and foot deformity. (b) Achilles tendon tightness and foot deformity. (c) Muscle MRI scan of the lower limbs shows diffuse involvement of the quadriceps muscles and relative sparing of the adductor compartments with relative hypertrophy of the adductor longus (white arrow) and semitendinosus muscle (black arrow) at the thigh level: at the calf level there is diffuse involvement with sparing of the anterior-medial muscles. (d) Brain MRI scan shows polymicrogyric pattern of frontal lobe cortex, sylvian fissure extending to the parietal lobe and thin corpus callosum.

Images (e)–(g) show SMA-LED caused by mutations in the BICD2 gene. (e, f) show wasting of both upper and lower leg typically seen in more severely affected individuals and the pes planus and pes cavus foot deformities commonly seen in this disorder (g). Muscle MRI scan of the lower limbs shows a common pattern of muscle involvement in individuals with mutations in BICD2 and DYNC1H1 lightface with variable fat replacement of muscles of the anterolateral thigh but relative sparing with or without relative hypertrophy of the semitendinosus muscle. At calf level there is diffuse involvement with sparing of the anterior-medial muscles.
The first gene associated with BVVLS/FLD was SLC52A3 and it encodes the human intestinal riboflavin transporter-2 (hRFT2). A second gene SLC52A2, encoding human riboflavin transporter-3 (hRFT3), a brain riboflavin transporter, has also been demonstrated to cause BVVLS as well as the SLC52A1 (GPR172B) gene, coding for human riboflavin transporter hRFT1.

The recognition of abnormal acylcarnitine profiles mimicking multiple acyl-CoA dehydrogenase deficiency in patients with BVVLS (Bosch et al. 2011) has elucidated a link between the putative function of SLC52A3 and SLC52A2 as riboflavin transporters and this neurodegenerative condition.

A recent study in a large cohort of patients carrying mutations in SLC52A2 has further defined the clinical presentation and the course in those carrying mutations in this gene (Foley et al. 2014). The most common presenting symptom is an ataxic gait, secondary to a progressive sensory neuropathy with parents reporting symptoms as early as age 7 months (nystagmus) and as late as age 8 years (ataxic gait): optic atrophy is frequently encountered in up to 93% of patients following formal ophthalmological evaluations. All patients have hearing loss with audiometry documenting bilateral sensorineural hearing loss while tongue fasciculations are also commonly found with evidence of a correlation between severity of fasciculations and length of time following the onset of first symptoms. Rapidly progressive upper limb weakness occurs after evidence of a sensory ataxic gait, with an initial pattern of weakness of neck extension and the distal upper limbs progressing to involve the proximal upper limbs. This pattern of weakness leads to a striking phenotype (sometimes referred to as ‘the child in a barrel syndrome’ characterised by maintenance of the ability to walk (with head and trunk support) despite subgravity upper limb and neck strength, resulting from the comparatively milder lower limb weakness in contrast to the severe involvement of axial and upper limb muscles (Fig. 24.2).

Respiratory muscle weakness leading to respiratory insufficiency can develop in the majority of individuals. Other clinical features observed include the absence of deep tendon reflexes and presence of a flexor plantar response. In a subset of patients the acute onset of weakness in the first few months of life can be preceded by respiratory failure, increased limb tone and increased tendon reflexes with clonus with neurogenic findings on EMG able to assist in suspecting this condition in these infants. Cognition is preserved despite significant visual and hearing impairments while inheritance is dominantly inherited.

Normal nerve conduction velocities have been reported in patients diagnosed with BVVLS although patients with mutations in SLC52A2 who presented with sensory ataxia had axonal sensorimotor neuropathy revealed by nerve conduction studies. The sural nerve biopsies from these patients show a preferential loss of large diameter myelinated axons which correlate with the clinical findings of absent deep tendon reflexes and the prevalent sensory ataxia.

Supplementation of riboflavin has demonstrated remarkable efficacy in a number of young patients both in patients with and without a plasma flavin deficiency, especially those treated early (Green et al. 2010; Bosch et al. 2011; Anand et al. 2012; Ciccolella et al. 2012; Koy et al. 2012). When untreated, BVVL is a severe disorder with a variable but mostly rapid downhill progression, especially in the younger age groups and with a possible fatal outcome.

### SPINAL MUSCULAR ATROPHY WITH RESPIRATORY DISTRESS

Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a form of SMA with respiratory distress due to diaphragmatic involvement (Grohmann et al. 1999, 2001). It has been recently renamed distal spinal muscular atrophy type 1 (DSMA1 MIM#604320) and is also known as hereditary motor neuropathy type 6 (HMN6) (Kaindl et al. 2008).

The exact prevalence of SMARD1 is unclear but studies have shown diaphragmatic palsy affects approximately 1% of patients diagnosed with early onset SMA (Giannini et al. 2006; Eckart et al. 2012) with currently more than 60 described. SMARD1 is caused by homozygous or compound heterozygous mutations in the immunoglobulin l-binding protein 2 (IGHMBP2) gene located on chromosome 11q13.2-q13.4 where frameshift deletion, in-frame deletion, non-sense, splice donor-site and recessive missense mutations have been described (Grohmann et al. 2001). The location and type of mutations do not appear to correlate with the severity of clinical features (Grohmann et al. 2003; Joseph et al. 2009).

As a result of mutations in the IGHMBP2 gene there is a degeneration of motor neurons in the anterior horns which explains the main phenotypical features of SMARD1, irreversible diaphragmatic palsy and progressive distal symmetrical muscular weakness (mainly of the lower limbs). Life expectancy is very low, with most patients dying within 13 months and only few surviving longer (Appleton et al. 2004; Pierson 2011).

Patients with a clinical picture similar to SMARD1 but without abnormalities in the IGHMBP2 gene have been described, suggesting the clinical phenotype can be caused by mutations in other genes currently unknown.

Extremely severe and rapidly progressive respiratory distress caused by diaphragmatic palsy is the main symptom of SMARD1 (Kaindl et al. 2008). The onset, usually within the first months of life, is often sudden and dramatic, needing prompt and irreversible invasive ventilation: the diaphragmatic palsy can be seen on a chest X-ray as an abnormal elevation of the dome of diaphragm. The eventration starts more often on the right side of the chest, probably because of pressure on the diaphragm by the liver (Grohmann...
et al. 1999, 2001, 2003). Early signs of the disease include weak cry, inspiratory stridor, difficulty eating and recurrent bronchopneumonia. Intrauterine growth delay, preterm and reduced fetal movements can often be seen as part of SMARD1 (Grohmann et al. 2003).

Unlike patients with proximal SMA, muscular weakness in patients with SMARD1 involves the distal muscles at first, often accompanied by congenital foot deformations which can lead to secondary finger contractures and fatty pads due to deposits of adipose tissue in the proximal phalanges, only later affecting the proximal muscles (Grohmann et al. 2003; Rudnik-Schoneborn et al. 2004). SMARD1 patients typically present a complete paralysis of the four limbs and later develop a progressive kyphoscoliosis while the deep tendon reflexes cannot be elicited in most affected individuals. Advanced SMARD1 often presents a significant autonomic involvement and symptoms can vary from cardiac arrhythmia to urinary retention needing catheterisation, bladder incontinence, excessive sweating and constipation (Grohmann et al. 2003; Pierson 2011).

Tongue fasciculations and facial weakness can also be present while the oculomotor neurons seem to be spared (Blaschek et al. 2014). In 2003 Pitt et al. proposed diagnostic criteria for SMARD1 based on clinical, histopathological and electrophysiological criteria with clinical criteria including low birthweight, onset of symptoms at birth with talipes and finger contractures or, by the age of 3 months, unilateral or bilateral diaphragmatic weakness, ventilator dependence within 1 month of onset and absence of dysmorphology or other conditions. The histopathological criteria included reduced myelinated fibre density and size without evidence of regeneration or demyelination on sural nerve biopsy, while electrophysiological criteria included evidence of distal denervation and severe slowing of conduction.

Figure 24.2 Phenotypic characteristics of Brown-Vialette-Van Laere syndrome caused by mutations in SLC52A2. Severe weakness of neck extension and upper limbs with comparatively less weakness of lower limbs seen in patients at different ages: (a) 1.8 years (b) 5.8 years and (c) 8.6 years. (d) Symmetrical atrophy of intrinsic hand muscles of left and (e) right hands at 10.5 years of age.
in one or more nerves (motor or sensory) (Pitt et al. 2003; Ruiz et al. 2005; Jedrzejowska et al. 2014).

There is no effective treatment available for SMARD1 with patients generally requiring mechanical ventilation. Antibiotic therapy and prophylaxis for recurrent airway infections and optimal nutrition are also very important (Jedrzejowska et al. 2014) while physical and occupational therapy are also essential aspects of the treatment.

Preclinical animal model studies have demonstrated a modest role for monoclonal antibodies with an agonist effect on the tyrosine kinase receptor C which is involved in the regulation of neuron plasticity and synaptic strength (Huang and Reichardt 2003; Ruiz et al. 2005). Neurotrophic factors such as insulin-like factor 1 (IGF1) have been considered as a possible candidate for future treatment trials as they seem to play an important role in the pathogenesis of SMARD1 (Krieger et al. 2014).

As for SMA, gene therapy mostly focuses on replacing the defective gene using self-complementary adeno-associated virus vectors (Foust et al. 2010; Passini et al. 2010; Valori et al. 2010; Dominguez et al. 2011). Apart from classic neonatal/infantile presentations there have been only a few reports of patients with an unusual display of symptoms (Guenther et al. 2004; Guenther et al. 2009; Joseph et al. 2009).

### JUVENILE AMYOTROPHIC LATERAL SCLEROSIS

Juvenile amyotrophic lateral sclerosis (JALS) is a form of chronic motor neuron disease with gradual weakness of voluntary muscles resulting from the destruction of neuronal cells, characterised by a combination of upper and lower motor neuron signs. The term JALS has been used for patients with onset of disease before 25 years of age who usually have a prolonged survival. It may be sporadic or familial (Ben Hamida et al. 1990) while the prevalence and incidence are not known: a relatively small number of patients have been reported to date but the disorder has been described in various ethnic groups. Onset is during childhood with a mean age of 6.5 years and reported range of 3–20 years. Patients then develop motor neuron degeneration leading to facial muscle spasticity, spastic dystarthis and spastic gait. Some patients are reported to have uncontrolled laughter and weeping (pseudobulbar syndrome) while mild atrophy of the legs and hands have also been observed in some individuals affected, with bladder dysfunction and sensory disturbances also found. The disease is usually slowly progressive and some patients have been reported to have become bedridden by 12–50 years of age. Mutations in the following genes have been found in patients presenting with JALS: ALS2 (2q33-q35), rarely SIGMARI (9p13.3), SPG11 (15q13-q15) and FUS (16p11.2). Mutations in the latter gene are sporadic and appear to be associated with a severe and aggressive course.

### X-LINKED INFANTILE SPINAL MUSCULAR ATROPHY (XL-SMA OR SMAX2)

SMA with X-linked inheritance is much rarer and more heterogeneous with an adult-onset form (SMAX1 or Kennedy disease, OMIM 313200) due to a triplet repeat expansion in the AR gene on Xq12 encoding the androgen receptor (La Spada et al. 1991) and an infantile-onset form (SMAX2, OMIM 301830) due to hemizygous missense mutations in the UBA1 gene on Xp11.23 encoding ubiquitin-activating enzyme 1 (Ramser et al. 2008).

X linked infantile SMA (XL-SMA) is a lethal disease characterised by severe hypotonia and areflexia with neurophysiological evidence of denervation and neuropathological findings of anterior horn cell loss in the spinal cord and brainstem. The clinical course is similar to the most severe forms of classic autosomal recessive SMA caused by mutations in the SMN1 gene, SMA type 0 and SMA type 1. The weakness in XL-SMA often has a prenatal onset manifesting with polyhydramnios and poor movements in utero, resulting in congenital contractures, especially digital contractures and possible fractures due to bone fragility. The course of the disease is progressive with no cognitive involvement reported so far, with other features variably presenting including micrognathia, kyphosis, scoliosis and cryptorchidism. Similarly to SMA1, the greatest difficulties in this disease are related to the respiratory complications in proportion to the weakness of the child, complicated by aspiration and frequent infections and children usually die by the age of 2 years as a result of respiratory failure (Iannaccone 2007). UBA1 is the only gene currently known in association with XL-SMA wherein the protein encoded by UBA1 catalyses the first step in ubiquitin conjugation to mark cellular proteins for degradation through the ubiquitin–proteasome system (UPS) (Tanaka 2004). The UPS pathway also plays an important physiological role in the degradation of the SMN protein implicated in autosomal–recessive SMA (Burnett et al. 2009).

Post mortem studies have demonstrated widespread involvement of the sensory system as well as developmental and degenerative cerebellar abnormalities, in addition to severe ventral motor neuron pathology while in contrast to typical SMN1-associated SMA the thalamus was unaffected. These findings indicate that SMAX2 would be more accurately classified as a motor sensory neuronopathy rather than a pure anterior horn cell disorder and that ubiquitin-proteasome pathway defects may not only cause neurodegeneration but also affect normal neuronal development (Dlamini et al. 2013).

Although UBA1 is the only gene currently known in association with XL-SMA there is evidence for locus heterogeneity as a linkage to the X chromosome region Xp11.3-q11.1 has been demonstrated in families with XL-SMA without mutations observed in UBA1 (Kobayashi et al. 1995).

### ARTHROGRYPOSIS MULTIPLE CONGENITAL

The term arthrogryposis multiple congenital (AMC) refers to the presence of joint contractures in at least two areas of
the body at birth with associated muscle wasting and fusiform joint configuration and results from reduced or absent fetal movement. It has an incidence of 1:3000 births and can occur in isolation, or as part of a syndrome. **Neurogenic arthrogryposis** due to dysgenesis of anterior horn cells of the spinal cord or motor nuclei in the brainstem is a rare variant with diverse clinical presentations (Clarren and Hall 1983).

AMC can overlap with other disorders including lethal and non-lethal Escobar variant, multiple pterygium syndromes, lethal congenital contracture syndromes and SMA type 1. At the milder end of the spectrum are the distal arthrogryposes in which contractures occur across the distal joints exclusively. Isolated AMC phenotypes arise as a result of mutations in genes encoding components required for (1) motor neuron structure, function and myelination (ADCY6, CNTNAP1, ECEL1, ERBB3, GLE1, PIP5K1C, SMN1 and TRPV4), (2) the neuro-muscular junction (CHAT, CHRNA1, CHRN1, CHRDG, CNTN1, DOK7, RAPSN and ZBTB42) or (3) skeletal muscle (ACTA1, DMPK, KLHL40, KLHL41, MYBPC1, MYH2, MYH3, MYH8, NEB, PIEZO2, RYR1, SYNE1, TNNT2, TNNT3, TPM2 and TTN) (Gupta et al. 2013; Laquerriere et al. 2014; McMillin et al. 2014; Patel et al. 2014).

Despite the large number of known disease-associated genes many patients with AMC remain without a genetic diagnosis. Although contractions may lead to worsening of function ability most children improve with physiotherapy, well-fitted orthoses and corrective surgery if indicated (van Bosse et al. 2007). A recent study conducted on 27 children suggests neurogenic arthrogryposis is usually a non-progressive disorder especially in the absence of concomitant brain abnormalities (Ambegaonkar et al. 2011).

The term **monomelic spinal muscular atrophy** or **Hirayama disease** refers to a peculiar muscular disease characterised by young age at onset (second or third decade), sporadic occurrence, male preponderance, weakness and atrophy affecting intrinsic muscles of hand and forearm usually confined to a single limb. Infrequently symptoms of cold paresis and hyperhidrosis are described with an abnormal sympathetic skin response (Gourie-Devi et al. 1984; Gourie-Devi and Nalini 2001; Gourie-Devi and Nalini 2003).

Hirayama disease of a unilateral upper extremity was first described in 1959, more commonly reported from Asian countries like Japan and India and thought to be rare in western countries despite patients being reported from Europe and America (Ghosh et al. 2011).

The characteristic appearance of oblique amyotrophy is a forearm amyotrophy sparing the brachioradialis muscle and relatively benign non-progressive course which differentiates it from motor neuron disease. In Hirayama disease weakness and wasting are noted in the small muscles of the hand along with preservation of the brachioradialis muscle with the weakness usually involving both extensors and flexors of fingers. Tremulousness of the hand on extension of the fingers (polyminimyoclonus) is often seen with most patients also reporting aggravation of weakness in cold weather (cold paresis). The pathogenesis is still unclear but according to various imaging and pathological studies the disease could be caused by dynamic compression of the lower cervical cord due to repeated or sustained neck flexion (Pradhan and Gupta 1997; Hirayama 2000; Hassan et al. 2012). The application of a hard cervical collar during the early phase of illness can halt the progression of illness (Verma et al. 2012).

### OTHER SMAs

#### SMA WITH PROGRESSIVE MYOCLOSTATIC EPILEPSY

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is a recently delineated, autosomal recessive lysosomal storage disorder caused by rare homozygous or compound heterozygous mutations in the N-acylsphingosine amidohydrolase 1 (acid ceramidase) **ASAH1** gene. It is characterised by motor neuron disease followed by progressive myoclonic seizures and generalised seizures with progressive neurological deterioration, mild to moderate cognitive impairment and eventual death due to respiratory insufficiency. The main clinical feature of this condition is the onset of motor deficits during childhood or at a juvenile age after normal developmental milestones. Progressive muscle weakness is caused by the involvement of lower motor neurons confirmed by EMG and/or muscle biopsy while myoclonic epilepsy is observed later and generally resistant to conventional therapy when the onset is in childhood. The disease course is progressive and leads to respiratory muscle involvement as well as severe disability or death occurring before 20 years of age (Zhou et al. 2012; Dyment et al. 2014).

Individuals with juvenile/adult onset show a slower and more benign evolution without cognitive impairment, with epilepsy and myoclonus responding to antiepileptic drugs. Other clinical features may include sensorineural deafness and tremor.

### ACQUIRED VARIANTS OF MOTOR NEURON DISEASE

The acquired motor neuron disorders are a heterogeneous group of conditions in which motor neuron degeneration or dysfunction produces the predominant manifestation of weakness while the sensory system is clinically spared. Such acquired motor neuron disorders may complicate metabolic, toxic or systemic disorders with the pathogenesis of such poorly understood and treatment mainly supportive. Paraneoplastic acquired motor neuron disorders may result from autoimmune directed against antigens shared by the affected neurons and associated cancer cells. Lower motor neuron syndrome (MNS) has been described in association with breast cancer and in a few patients following radiation therapy in the course of cancer (Sadowsky et al. 1976; Ferracci et al. 1999).
SMA-LIKE DISORDER DUE TO SCO2 MUTATIONS

A possible pathogenic role of mitochondria in SMA has been proposed (Berger et al. 2003). Infants with deficiency of cytochrome c oxidase (COX) due to SCO2 mutations have been reported with a mild SMA-like phenotype associated with atypical neurological symptoms, as well as increase of lactate in plasma, cerebrospinal fluid or urine. In a recent study a homozygous mutation in the SCO2 gene was reported causing a SMA-like presentation with stridor and respiratory insufficiency (Pronicki et al. 2010).

Spinal muscular atrophies are inherited neuromuscular diseases characterised by degeneration of spinal cord motor neurons resulting in progressive muscular atrophy and weakness. The most common forms, those likely to be encountered by any paediatric neurologist, are linked to mutations in SMN1 (5q-SMA) with a wide clinical spectrum ranging from early infant death to normal adult life with only mild weakness. The care for spinal muscular atrophies requires a multidisciplinary approach and consensus reached on several aspects of care: this has enabled a more proactive role of anticipatory care, targeting disease-specific complications and resulting in a substantial effect on the disease prognosis, even for more severe forms. The recent progress in the understanding of molecular pathogenesis of SMA and advances in medical technology are inducing the development of a number of novel and exciting therapeutic approaches. At the time of writing several novel strategies are being tested in clinical trials.

Non-5q associated spinal muscular atrophies, the most common condition represented by the genetically heterogeneous group of SMA with lower-limb-predominant weakness, share recognisable clinical features and a slowly or non-progressive course. A less common but treatable condition is the BVVL syndrome which should be suspected in the presence of early onset weakness with respiratory failure associated with sensory ataxia, bilateral sensorineural hearing loss and later progressive pontobulbar palsy and/or predominant upper limb weakness. Treatment with riboflavin should be considered even while genetic confirmation is in progress.

Following the recent genetic advances it is likely the spectrum of these rare disorders will be further widened. However, the clinical presentation, with particular emphasis on the distribution of weakness and the pattern of inheritance, can help in differentiating the less common motor neuron diseases and guide the clinician toward a possible genetic confirmation.

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## Disorders of the Peripheral Nerves

*Manoj Menezes and Robert Ouvrier*

### Charcot–Marie–Tooth Disease (Hereditary Motor and Sensory Neuropathy)

*Clinical Features of CMT*  
*Classification of CMT Types*  

**CMT1/HMSN1**  
**X-Linked CMT**  
**Autosomal Recessive Demyelinating Types of Charcot–Marie–Tooth (CMT4; Autosomal Recessive HMSN Type I)**  
**CMT2/HMSN II**  
**Severe Infantile Axonal Neuropathy with Respiratory Failure**  
**CMT3/HMSN III or Dejerine-Sottas Disease**  
**Classic Phenotype**  
**Congenital Hypomyelinating Neuropathy**  
**Dominant Intermediate CMT**

### Uncommon Neuropathies with Motor and Sensory Involvement

- Hereditary Neuropathy with Liability to Pressure Palsies
- Hereditary Neuralgic Amyotrophy (Brachial Plexopathy)
- Thermosensitive Neuropathy

### Hereditary Sensory and Autonomic Neuropathies

- HSAN1 (Sensory Radicular Neuropathy)
- HSAN2 (Congenital Sensory Neuropathy)
- HSAN3 (Familial Dysautonomia or Riley-Day Syndrome)
- HSAN4 (Congenital Insensitivity to Pain with Anhidrosis)
- HSAN5
- Other Forms of HSAN with Insensitivity or Indifference to Pain

### Recommendations for Genetic Testing in CMT

### Complex Neuropathies Associated with Central Nervous System Involvement and Metabolic Neuropathies

- Hereditary Motor and Sensory Neuropathy with CNS Involvement
- Giant Axonal Neuropathy
- Refsum Disease (HMSN IV) (Heredopathia Atactica Polyneuritiformis)
- Brown-Vialetto-Van Laere Syndrome due to Riboflavin Transporter Deficiency
- Other Neuropathies with a known Metabolic Abnormality
- Mitochondrial Neuropathies

### Acquired Diffuse Neuropathies

- Acute Inflammatory Neuropathy, Acute Polyradiculoneuritis, Guillain–Barré Syndrome and Related Disorders
- Pathology
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This chapter considers only those disorders in which the primary pathological process affects the axons of motor or sensory cells or both, or their myelin sheaths and associated Schwann cells. Diseases in which axonal damage results from primary lesions of the neuronal cell body have been described in Chapter 24. Hereditary neuropathies most often involve both sensory and motor fibres, though they may be purely motor or sensory in nature, or may predominantly affect one fibre type. Nerve fibre function can be disturbed in several manners (Fig. 25.1). Wallerian degeneration occurs when an axon is separated from the cell body or when the cell dies.

Axonal neuropathies are characterised primarily by involvement of the axon and may be the result of genetic disease, toxins, vascular disease and so on. In many cases, axonal neuropathies begin and remain more severe distally than proximally, perhaps because the enormous length of axons makes the metabolic needs of their most distal parts difficult to meet. This may also be due to disturbances in the axonal transport systems. In axonal neuropathies, nerve conduction velocities are normal or only slightly slowed despite evidence of denervation. Characteristically, the amplitude of sensory and compound muscle action potentials is reduced.

Diseases of the Schwann cell and the myelin sheath are also due to multiple (genetic or acquired) causes, especially inflammatory diseases. The lesions are diffuse or segmental, that is, limited to lengths of nerve depending on one Schwann cell (internode). Such a process may produce a conduction block or a slowing of nerve conduction velocities, either focal or generalised. Slowing may be diffuse and uniform as in some metabolic and hereditary neuropathies (Miller et al. 1985). Conduction block and temporal dispersion are indicative of multifocal segmental demyelination. Conduction block is defined at the cellular level as failure of an action potential to propagate throughout the length of an axon. When many individual axons are blocked, especially at a localised site, both the amplitude and the area under the curve of the evoked muscle action potential are reduced when proximal stimulation is compared to distal stimulation (beyond the region of conduction block) of the motor nerve. With pure temporal dispersion, increased duration of the evoked muscle action potential occurs, together with reduced amplitude but the area under the curve is preserved. Demyelination and axonal disease are not independent processes, but the exact nature of their relationship remains unclear. Inherited neuropathies may involve the peripheral nervous system exclusively or predominantly affect the peripheral nervous system (Charcot–Marie–Tooth disease) or may occur as part of a syndrome complex that involves the central nervous system (CNS) as well as other non-neurological organs.

Charcot–Marie–Tooth disease (CMT) is a group of genetically heterogeneous disorders that affect peripheral nerve function; CMT is named after Jean-Martin Charcot, Pierre Marie and Henry Tooth who originally described the disorder in 1886. CMT is the most common inherited neuromuscular disorder, affecting approximately one in 2500 individuals (Skre 1974) and accounting for approximately 40% of childhood chronic neuropathies (Ouvrier 1992). Degeneration of the axon, its myelin sheath, or both, results in progressive symmetrical distal weakness, sensory loss and areflexia. CMT is caused by disorders of genes with functions that vary from compaction and maintenance of myelin, to cytoskeletal formation, axonal transport and mitochondrial metabolism (Pareyson and Marchesi 2009). Inheritance may be autosomal dominant, autosomal recessive, X-linked or mitochondrial.

Clinical Features of CMT

While genetically heterogeneous, the classic CMT phenotype is broadly similar and characterised by gait difficulties, foot deformity, sensory loss and wasting of the distal muscles in the hands and feet (Ouvrier et al. 1999; Pareyson and Marchesi 2009). Age at onset may vary from soon after birth to the sixth and seventh decades of life, though most commonly is in the first two decades of life, and severity of disease may vary greatly. Irrespective of whether the genetic cause affects myelin...
or axon function, axonal degeneration results and correlates with severity of weakness. This axonal degeneration affects the longest fibres first, and hence symptoms usually begin distally, and in the lower limbs before the upper limbs (Pareyson and Marchesi 2009).

Children usually present with gait disturbance or foot deformity. Pes cavus is typical and is often associated with hammer toes. Pes cavus has been attributed to imbalance between the long flexors and invertors of the ankle but involvement of the intrinsic muscles of the feet may be more important (Gallardo et al. 2006). Some children present with pes planus and marked valgus deviation of the feet. Gait disturbances include high-stepping gait, difficulties running, frequent falls or unsteadiness. Symptoms progress slowly and it may take a number of years before children are brought to medical attention. Examination reveals symmetrical atrophy of the peroneal muscles (hence the term peroneal amyotrophy classically applied to CMT), later involving the calves and eventually the lower third of the thigh (Fig. 25.2). In the upper extremity, atrophy of the small muscles of the hand may occur (claw hand – main en griffe) and weakness of the intrinsic muscles of the hands is more often demonstrable. Tendon reflexes are decreased or absent (Ouvrier et al. 1999). Sensory loss is characterised by abnormalities of touch, proprioception and vibration and by sensory ataxia. Dysoesthesiae or shooting pains are not a feature, although pain due to foot deformities or calluses may be severe in some patients. Muscle cramps are not uncommon. Vasomotor disturbances are common, with frequent cyanosis and marbling of the skin.

**Classification of CMT Types**

CMT affects both sensory and motor peripheral nerves and is hence also called hereditary motor and sensory neuropathy (HMSN). In addition, types that affect predominantly sensory fibres (hereditary sensory neuropathy [HSN]) or predominantly motor fibres (hereditary motor neuropathy [HMNI]) have been identified. CMT is classified based on these neurophysiological and histopathological characteristics and mode of inheritance, and this classification, together with phenotypic clues, is used to direct genetic testing. The availability of next-generation sequencing technologies, including whole-exome, whole-genome and disease-specific gene panels
promises to revolutionise genetic testing for CMT and its classification system. As the number of gene disorders causing CMT grows, it is increasingly recognised that there exists significant phenotypic and genotypic crossover between various CMT types.

Based on upper limb motor conduction velocities (MCV), CMT is divided into a demyelinating form, CMT1 (MCV < 38m/s) and axonal form, CMT2 (MCV > 38m/s in adults) (Harding and Thomas 1980a). Demyelinating CMT with an autosomal recessive inheritance is classified as CMT4. An intermediate form with motor conduction velocities between CMT1 and CMT2, in the range of 25–45m/s has also been identified. CMT3 (Déjerine–Sottas neuropathy) refers to severe, early-onset neuropathy with delayed motor milestones and hypomyelination on nerve biopsy and has now been shown to be caused mainly by point mutations of genes causing CMT1. Further classification is based on the identified gene or locus; for example, autosomal dominant genes causing CMT1. Further classification is based on the pattern of inheritance and the causative gene, where known, being incorporated in the subtype designation (Mathis et al. 2015) (Table 25.1). In this Chapter, the traditional nomenclature will be utilised, as the proposed new nomenclature has not yet been officially adopted.

**CMT1/HMSN1**

CMT1 is the most common demyelinating disorder, representing 70% of all demyelinating CMT in adults (Nelis et al. 1996). The prevalence of CMT1 is 3.8 per 100,000 population, accounting for about 50% of paediatric cases of hereditary neuropathies (Hagberg and Westerberg 1983). Onset of CMT1 is usually within the first decade, although cases of later onset are known. CMT1 is genetically heterogeneous but more than 80% of childhood cases are linked to chromosome 17 (CMT1A). The defect in such cases is usually a submicroscopic duplication, approximately 1.5 megabases in length, within band 17p11.2 (Raeymaekers et al. 1991). The duplication includes the *PMP22* gene encoding peripheral myelin protein 22 (Patel et al. 1992) so that the gene is present in three copies. The duplication is thought to result from unequal crossing-over during meiosis. Deletions of the same region result in hereditary neuropathy with liability to pressure palsies (HNPP). Cases of CMT1A due to trisomy 17 have also been recorded. The mechanism by which overexpression of *PMP22* (whether produced by having three copies of the *PMP22* gene or by a gain of function mutation) produces the clinical manifestations is not understood.

A very early onset during the neonatal period or the first year is not as rare as once thought in CMT1 and specifically in CMT1A (Ouvrier et al. 1987; Baets et al. 2011). Asymmetrical and even unilateral involvement has been rarely reported. Cases of CMT1 are not uncommonly associated with tremor of the upper limbs and sometimes with some degree of clumsiness. Hypertrophy of the calves occurs in some families (Uncini et al. 1994). Deep tendon reflexes, especially the ankle reflexes, are often lost early, and this may be a useful sign for the clinical diagnosis of the condition in young children with affected relatives or in parents of children with the disease (Garcia et al. 1998). Scoliosis, lordosis, hip dysplasia, metatarsal stress fractures and recurrent patellar dislocation may occur (Harding and Thomas 1980a; Thomas et al. 1997). Palpable nerve enlargement is not rare in children but is difficult to assess objectively. Ultrasound neurography is useful for detection (Yiu et al. 2016). The CSF protein level is elevated in over half the cases, but lumbar puncture is not indicated.

Progression of CMT1A is slow, and long periods of stability are common. Most patients remain ambulant but some severe cases exist. In an occasional patient, intercurrent infections or rapid growth may be associated with acceleration of the disease process. Pregnancy may cause significant deterioration (Gastaut et al. 2000), and exposure to vincristine can cause a severe regression (Igarashi et al. 1995). Rare cases of proven CMT1 with rapid deterioration and response to steroid treatment are on record (Dyck et al. 1993).

**Diagnosis of CMT1**

The diagnosis of CMT1 is easy in typical forms. The presence of sensory deficit is important to distinguish the condition from distal forms of myopathy or spinal amyotrophy. Slowing of motor and sensory nerve conduction velocities to less than 60% of the lower limit of normal values and increased distal latencies separate CMT1 from CMT2. There is no correlation between slowing of conduction velocities and clinical severity. Nerve conduction abnormalities appear early and are present in most children with CMT1A by 3 years of age (Ouvrier 1992) or even earlier (Berciano et al. 1989), although they are sometimes inconclusive (Ryan and Jones 2004). Prolongation of distal latencies may precede slowing of nerve conduction (Garcia et al. 1998). When inherited from a parent, conduction velocities are usually abnormal in the carrier parent, whether or not clinically affected. Neurogenic electromyography (EMG) changes are usually mild to moderate. Approximately 20% of affected individuals have a significant disability and a similar proportion remain asymptomatic.

Testing of DNA for the presence of the chromosome 17p11.2 duplication achieves a genetic diagnosis in most cases. When negative, sequencing of *MPZ* and *PMP22* should be pursued. Diagnostic testing for other genes causing CMT1 (Table 25.1) is often available only on a research basis, but the recent development of neuropathy-specific gene panels has altered this approach of sequencing genes based on the population frequency and phenotypic clues.
### Table 25.1  New proposal for designation of Charcot–Marie–Tooth diseases, distal hereditary motor neuropathies and hereditary sensory and autonomic neuropathies

<table>
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<tr>
<th>Current denomination</th>
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Continued
Table 25.1  New proposal for designation of Charcot–Marie–Tooth diseases, distal hereditary motor neuropathies and hereditary sensory and autonomic neuropathies (continued)

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Continued
Nerve biopsy is not specific and is not necessary for diagnosis, especially when there is a clear family history of the disease. The main indication for biopsy would be differentiation from chronic inflammatory neuropathy. In such cases, nerve biopsy and/or a trial of steroid treatment may be warranted.

Although the penetrance of the disease is high (83%), there is significant variability in clinical and pathological expression.
In some cases, the clinical and even nerve biopsy findings can be minimal, particularly in young children. Nevertheless, children affected by CMT1A almost always show some manifestations by the age of 3 years. Mild and even asymptomatic cases occur (Thomas et al. 1997) and systematic examination of parents and relatives, therefore, improves the diagnostic yield.

In children without the duplication, point mutations of the \textit{PMP22} (also classified as CMT1A) and \textit{MPZ} (myelin protein zero) (CMT1B) genes have been found (Roa et al. 1993; Warner et al. 1996). Mutations of both the \textit{PMP22} and \textit{MPZ} genes cause a variety of clinical pictures, ranging from congenital hypomyelination and Déjerine–Sottas phenotype to a CMT1A-like phenotype. \textit{MPZ} may also cause late-onset axonal (CMT2I and J) and rarely, intermediate forms of CMT (CMTDID). Deafness (PMP22 and MPZ) and pupillary abnormalities (MPZ) may be associated (De Jonghe et al. 1999; Wilmshurst and Ouvrier 2011). Mouse and rat models that overexpress \textit{PMP22} develop phenotypic features consistent with CMT1A, and the severity of demyelination is proportional to the level of \textit{PMP22} expression. \textit{PMP22} comprises only 2–5% of peripheral nervous system myelin. Impaired cellular trafficking appears to be a possible mechanism in \textit{PMP22}-related neuropathies (Lupski and Chance 2005). \textit{MPZ} constitutes about 50% of myelin protein and is important for the process of myelin adhesion (Shy 2005).

Less frequently, mutations in \textit{LITAF/SIMPLE} (CMT1C), a gene that may be involved in aberrant protein degradation, and zinc finger transcription regulator \textit{EGR2} (CMT1D), encoding Krox20/EGR2, a transcription factor regulating expression of a number of myelin-related genes, may also cause CMT1 (Warner et al. 1999; Street et al. 2003). Homozygous \textit{EGR2} mutations also cause a more severe autosomal recessive hypo- and demyelinating neuropathy CMT4E.

**Pathology of CMT1**

The pathology of CMT1 has been studied mainly by muscle and nerve biopsy. CMT1 is characterised pathologically by extensive segmental demyelination and remyelination with the development of ‘onion bulbs’ around nerve fibres (Gabreëls-Festen et al. 1992). Only a few postmortem examinations have been reported: these cases showed degeneration of the posterior columns, some loss of anterior horn cells, and degeneration of the anterior and posterior spinal roots (De Recondo 1975). There is a reduction in the numbers of myelinated fibres, with the greatest loss among those of large calibre. The distribution of fibre diameters is thus unimodal. Unmyelinated fibres are not affected. Proliferation of the sheath of Schwann produces the classic ‘onion bulb’ formations (Fig. 25.3) that can be shown by electron microscopy to contain only Schwann cells and their processes. Nerve fibre teasing shows numerous images of segmental and paranodal demyelination and remyelination, predominating in the distal part of nerves. Pathological lesions, in particular onion bulbs, are nonspecific and indicate only the succession of demyelinating and remyelinating episodes that can also be observed in many other neuropathies. When marked, the process leads to hypertrophy of nerve roots and plexuses. Degenerative changes in muscle are secondary to neural damage. The histopathological findings of CMT1B, due to \textit{MPZ} mutations, are similar to those of CMT1A but uncompacted myelin may be seen in a significant number of fibres, and focal folding of myelin (tomacula) can also be prominent.

**X-LINKED CMT**

There are currently six known loci associated with X-linked CMT (CMTX) (Kennerson et al. 2013; Timmerman et al. 2014), which makes up approximately 10% of adult cohorts with CMT (Murphy et al. 2012). The most frequent X-linked form is CMTX1 caused by mutations in the \textit{GJB1/Cx32}
(gap junction beta 1/connexin 32) gene (Bergoffen et al. 1993), encoding a membrane-spanning gap junction protein localised adjacent to the nodes of Ranvier and the Schmidt–Lanterman incisures. Pedigrees show the expected absence of male-to-male transmission. Males are usually much more obviously affected than females but generally clinical involvement is less severe in the first decade than in those with CMT1A. On the other hand, the eventual degree of disability is greater in mature males with CMTX than in CMT1A. Occasional affected children may present with isolated deafness (Stojkovic et al. 1999) and some have had transient CNS symptomatology associated with white matter lesions (Hanemann et al. 2003). The neurophysiological features of the X-linked type in males may resemble those of CMT1A, but average motor conduction velocity (MCV) is about 10m/s faster in CMTX males (mean peroneal MCV 31m/s) than in CMT1A males (mean peroneal MCV 22m/s) (Nicholson and Nash 1993) whereas in females they may be in the axonal range. Most ‘intermediate’ types of CMT with mildly slowed conduction velocities are X-linked.

There are other rare forms of inherited neuropathy linked to the X chromosome. Of these, CMTX2 (linked to Xp22.2), CMTX4 (Cowchock syndrome, due to mutations in AIFM1) and CMTX5 (due to mutations in PRPS1) are syndromic inherited neuropathies, often associated with intellectual disability, and it has been argued that they should not be classified as CMT (Cowchock et al. 1985; Ionesescu et al. 1992; de Brouwer et al. 2010). CMTX3 has been linked to Xp26.3–27.1 and has recently been shown, using whole genome sequencing, to be due to a 78kb insertion from 8q24.3 while CMTX6 is caused by mutations in the PDK3 gene (Kennerson et al. 2013; Brewer et al. 2016).

In CMTX, the pathological lesions vary from predominant chronic de- and re-myelination to, more commonly, a mixture of demyelination and axonal degeneration with moderate loss of myelinated fibres (Sander et al. 1998).

**AUTOSOMAL RECESSIVE Demyelinating Types of Charcot–Marie–Tooth (CMT4; Autosomal Recessive HMSN Type I)**

CMT4 includes the group of autosomal recessive demyelinating neuropathies (Table 25.1). All are rather severe, early-onset disorders with moderately slow motor conduction velocities (usually around 20m/s with a range 3–37m/s). As expected with recessive inheritance, affected children may have similarly affected siblings and clinically unaffected parents who may be related. Recent reports have shed light on clinical and molecular findings in a number of these conditions and have provided some insight into their relative frequency. North African and Middle Eastern populations appear to show a higher prevalence of recessive CMT.

**CMT4A** is caused by mutations in the **GDAP1** (ganglioside-induced differentiation-associated protein-1) gene, which is involved in mitochondrial fission (Niemann et al. 2005). Most patients show an early-onset severe phenotype with prominent foot deformities (Nelis et al. 2002). There is rapidly progressive weakness and sensory loss that involves the lower and then upper limbs, resulting in loss of ambulation in the second and third decades of life. The clinical spectrum of this disorder has been expanded by the recognition that patients with GDAP1 mutations may develop laryngeal and diaphragmatic paralysis in later life (Birouk et al. 2003; Stojkovic et al. 2004; Claramunt et al. 2005). GDAP1 mutations may cause demyelinating or axonal degenerative changes in nerve biopsies in different kindreds (Di Maria et al. 2004; Stojkovic et al. 2004). GDAP1 mutations may also cause recessive axonal and intermediate CMT, or rarely, autosomal dominant CMT (Tazir et al. 2013).

**CMT4B1** and **CMT4B2** are characterised by the presence, on biopsy, of striking in- and out-foldings of myelin, although this finding is not invariably (Quattrone et al. 1996; Parman et al. 2004). Both disorders are associated with mutations of members of the myotubularin family. CMT4B1 is caused by mutations in the **MTMR2** (myotubularin-related protein-2) gene which is involved in membrane trafficking (Previtali et al. 2007). Affected individuals have an early onset of mainly distal weakness followed by proximal weakness and wasting (Tazir et al. 2013). Deep tendon reflexes are usually absent even in the early stages. Sensory changes are difficult to detect in infancy but are usually evident later in childhood. Most cases have pes cavus. Ptosis, and internal and external ophthalmoplegia are reported. Facial nerve weakness may give rise to pouting lips. Dysphagia, vocal cord paresis, dysarthria, ataxia and nocturnal hypoventilation may occur later. The clinical course is usually more severe than in CMT1A. Scoliosis is frequent. Many adults are wheelchair-dependent and several have died in the fourth and fifth decades.

Apart from the myelin disturbance, CMT4B2, due to mutations in the **SBF2/MTMR13** (set-binding factor/myotubularin-related protein-13) gene, is usually associated with congenital or juvenile glaucoma (Azzedine et al. 2003; Senderek et al. 2003b), although some kindreds lacked this feature (Hirano et al. 2004). Excessive myelin unfolding may also be seen with **MPZ, PRX** and **FGD4** mutations (Tazir et al. 2013).

**CMT4C**, due to mutations in the **SH3TC2** (SH3 domain and tetratricopeptide repeat domain 2) gene, important for regulation of endosomal recycling, is characterised by early-onset scoliosis that may predate the neuropathy by many years (Yger et al. 2012). Onset is usually in the first decade and while some patients progress slowly, allowing ambulation up to the fifth decade, others become wheelchair-dependent during their adolescent years (Senderek et al. 2003a). Nerve conduction velocities range from 4m/s to 37m/s. A remarkable difference in conduction slowing between nerves of the same limb, conduction block and dispersion of CMAPs may be seen (Yger et al. 2012). Histopathologically, nerve biopsies characteristically reveal basal lamina onion
bulbs and extended Schwann cell cytoplasmic processes around unmyelinated fibres. Giant axons may also be seen (Vallat et al. 2005).

CMT4D (HMSN-Lom) is the commonest of three recessively inherited polyneuropathies that are largely confined to inbred Roma (Gypsy) populations. HMSN-Lom was originally identified in ‘travellers’ living in the city of Lom, Bulgaria. It is due to mutations of the NDRG1 (n-myc downstream-regulated gene 1) gene, which plays an important role in Schwann cell trafficking and endosomal transport (King et al. 2011). The clinical picture is similar to other autosomal recessive demyelinating neuropathies but deafness commonly supervenes after the first decade (Kalaydjieva et al. 2000).

CMT4E is a rare neuropathy attributed to homozygous mutations of the EGR2 (early growth response 2) gene that can produce a Déjerine–Sottas or congenital hypomyelinating neuropathy phenotype (Warner et al. 1999). Nerve conduction velocities are very low, often less than 5m/s.

CMT4F is caused by mutations of the PRX (periaxin) gene which is considered important for the formation and maintenance of peripheral nerve myelin. Patients usually have an early-onset Déjerine–Sottas phenotype but progression can be slow (Boerkoel et al. 2001; Guilbot et al. 2001). Sensory involvement with dysaesthesiae and ataxia may be prominent. Nerve conduction velocities tend to be very slow (2–3m/s). Nerve biopsies have shown a severe loss of myelinated fibres with many onion bulbs and some fibres with myelin outfoldings. Mice lacking periaxin show similar histopathological findings.

CMT4G (HMSN-Russe) is another of the neuropathies seen in the European Roma population. It is similar to CMT4D except for later occurrence of deafness and slower progression (Navarro and Teijeira 2003). It has been mapped to 10q22 and the gene has been identified to be HK1 (hexokinase 1) (Hantke et al. 2009). The nerve biopsy shows loss of large myelinated fibres and prominent clusters of regenerated axons (Thomas et al. 2001).

CMT4H is caused by mutations of FGD4 (FGD1-related f-actin-binding protein), which encodes the Rho GTPase guanine nucleotide exchange factor, frabin, and has an important role in myelin development and maintenance (Stendel et al. 2007). Affected individuals have an early-onset sensorimotor neuropathy with slow progression, remaining ambulant into middle age.

CMT4J is caused by mutations in Fig4, which encodes a phosphatidylinositol 3,5-bisphosphate involved in cycling of intracellular organelles (Chow et al. 2007). Onset may vary from early childhood or as late as the sixth decade, and may show slow gradual deterioration or rapid progression. Proximal weakness is seen early and may result in wheelchair dependence as early as the third decade of life (Nicholson et al. 2011; Menezes et al. 2014). Asymmetrical involvement of the extremities and rapidly progressive involvement of a single limb resembling chronic inflammatory demyelinating neuropathy have also been described (Cottenie et al. 2013). Nerve conduction studies show combined axonal and demyelinating features, often with MCV less than 20m/s.

It has been suggested that CMT4A may constitute up to 25% of cases of autosomal recessive CMT, but only one GDAP1 mutation was detected in a study of 20 Turkish patients with probable autosomal recessive early-onset demyelinating neuropathy who were carefully studied with screening for nine possible causative genes. The other five proven mutations included two cases of MTMR2, and one each of SH3TC2, NDRG1 and PRX mutations. Thus, no mutation was detected in 14 of the 20 patients (Parmar et al. 2004). In a similar study in Japan, three of 66 patients with CMT4 were found to have PRX mutations (Kijima et al. 2004).

CMT2/HMSN II

CMT2 also produces a clinical picture consistent with the phenotypic description of CMT disease. Its frequency in children is classically much lower than that of CMT1 (Ouvrier 1992; Ouvrier et al. 1999; Ouvrier and Wilmshurst 2003). Data from our clinic show that CMT2 makes up 20% of all childhood CMT. Autosomal dominant and recessive forms of CMT2 have been described.

Clinical Features of CMT2

The clinical manifestations are similar to those of CMT1 but often have a later onset, during the second or third decade. Atrophy of posterior tibial and calf muscles is commonly as marked as in the anterolateral compartment. Absent reflexes and foot deformity are less frequent than in CMT1, but foot ulcers may occur making certain subtypes, such as CMT2B, difficult to distinguish from hereditary sensory and autonomic neuropathy (HSAN) type I (see HSAN1 [Sensory Radicular Neuropathy] section) (Elliott et al. 1997). There is no nerve hypertrophy and raised CSF protein is rare. Upper limb tremor is uncommon (Salisachs et al. 1979; Harding and Thomas 1980a; Westerberg et al. 1983). Differentiation from CMT1 is by electrophysiological investigation. Motor and sensory conduction velocities are normal or only mildly decreased. In CMT patients over 2 years of age, a motor conduction velocity more than 38m/s in the median nerve is compatible with the diagnosis of CMT 2, whereas values less than 38m/s are more in favour of CMT1 (Harding and Thomas 1980a; Quattrone et al. 1996).

Heterogeneity of CMT2

CMT2 has been linked to at least 22 loci and 20 genes (Table 25.1). While CMT2A was initially linked to a missense mutation in the KIF1B (kinesin family member 1B) gene in one pedigree, no such mutations have been identified in other affected kindreds. Mutations in the gene encoding a mitochondrial fusion protein, MFN2 (mitofusin 2) are
responsible for around 20% of CMT (Zuchner et al. 2004; Kijima et al. 2005). There is wide phenotypic heterogeneity, with some patients having an early onset and rapid progression resulting in loss of ambulation in early adulthood, while others have a late-onset, slow progression and preserved ambulation (Feely et al. 2011; Bombelli et al. 2014). Optic atrophy and vocal cord paresis may be associated, and presentation may be as a pure motor neuropathy. Sural nerve biopsy shows axonal degeneration with small rounded abnormally aggregated mitochondria, with irregular inner and outer mitochondrial membranes and disrupted cristae (Funalot et al. 2009). Some families may have an early-onset severe neuropathy due to the presence of compound heterozygous MFN2 mutations (Nicholson et al. 2008). Mitochondria undergo continued cycles of fission and fusion of their inner and outer membranes. MFN2 is a large mitochondrial GTPase. It may function to tether mitochondria before fusion. The neuropathy may thus be due to a defect in mitochondrial fusion/fission that interferes with energy production and slows axonal transport.

CMT2B is caused by missense mutations in the small GTPase late endosomal protein RAB7, which may have a role in axonal transport (Houlden et al. 2004). It may be difficult to differentiate clinically from HSAN1, due to mutations in SPTLC1, because of the presence of moderate sensory loss with complicating ulcers in up to 50% of cases (Verhoeven et al. 2003).

CMT2C, a condition clinically characterised by diaphragm, intercostal and vocal cord paralysis, has been shown to be caused by mutations in the cation channel gene TRPV4 (transient receptor potential cation channel subfamily V member 4), a member of the large family of cation selective channels involved in sensory stimulus transduction (Klein et al. 2011b). The phenotypes associated with TRPV4 mutations may vary from CMT2C to congenital spinal muscular atrophy and scapuloperoneal spinal muscular atrophy (Deng et al. 2010).

CMT2D, which causes prominent weakness of the hands usually commencing in adolescence has been localised to chromosome 7p15 and is due to mutations of the GARS (glycyl aminoacyl tRNA synthetase) gene, which may also cause a syndrome of distal spinal muscular atrophy (SMA type V) (Antonellis et al. 2003). In contrast to the usual presentation of CMT as a length-dependent neuropathy, with the lower limbs being affected before the upper limbs, mutations in GARS and BSCL2 may cause a predominant distal upper limb weakness with later and less severe involvement of the lower limbs (Rohkamm et al. 2007). Mutations in the genes encoding a number of amino-acyl tRNA synthetases have been reported to cause CMT. These include AARS (CMT2N), YARS (DICMTC), KARS (CMTRIB), MARS and HARS (Jordanova et al. 2006; Latour et al. 2010; McLaughan et al. 2010; Gonzalez et al. 2013; Vester et al. 2013).

CMT2E is due to mutations of the NEFL (neurofilament light) gene. Nerve conduction velocities may span the demyelinating and axonal degenerative range. Cases with slow nerve conduction velocities have been classified as having CMT1F, while those with velocities in the axonal range have been grouped as CMT2E. Onset in those with slow nerve conduction is often before the age of 13 years and the nerve biopsy in one individual showed a mixed axonal/demyelinating picture (Jordanova et al. 2003).

CMT2L and CMT2F are caused by mutations in the genes encoding the heat-shock proteins HSPB1 and HSPB8 (also called HSP27 and HSP22). The heat-shock proteins are stress proteins induced in response to a variety of physiological and environmental factors (Evgrafov et al. 2004; Tang et al. 2004; Tang et al. 2005). Affected individuals present with the adult onset of distal weakness, mild sensory loss and foot deformity. CMT2I and CMT2J refer to axonal neuropathies caused by certain mutations of the MPZ gene (De Jonghe et al. 1999; Auer-Grumbach et al. 2003). CMT2K is caused by dominant GDAP1 (ganglioside-induced differentiation-associated protein-1) and is allelic to CMT4A. Dominant GDAP1 mutations are rare and cause a later-onset mild axonal neuropathy (Zimon et al. 2011).

### Autosomal Recessive Forms of CMT2

Although autosomal recessive CMT of axonal degenerative types are known, few have been fully elucidated. LMNA mutations have been shown to cause CMT2B1, in addition to a variety of other syndromes including muscular dystrophy, lipodystrophy and premature ageing (Benedetti et al. 2007). The LMNA gene encodes the lamin A and C proteins, intermediate filaments that are components of the inner nuclear membrane. This recessive neuropathy has been described in Algerian and Moroccan families from North Western Africa, with a strong founder effect for the R298C mutation (De Sandre-Giovannoli et al. 2002). Onset is from childhood to early adulthood, and the phenotype may vary from classic to severe CMT, with varying rates of progression (Bouhouche et al. 2007). Rarely, other mutations have been described beyond this ethnic group, often in association with a myopathy (Goizet et al. 2004; Benedetti et al. 2005). Mutations in HINT1 (histidine triad nucleotide-binding protein 1) cause recessive axonal neuropathy with neuromyotonia (NMAN). Affected patients have a motor-predominant neuropathy with disease onset in childhood, action myotonia and neuromyotonia on EMG.

The series of axonal neuropathies described by Ouvrier et al. (1981) and Gabreëls-Festen et al. (1991) included a number of autosomal recessive cases with a distinctive clinical phenotype at a time when recessive cases were not included in the Dyck classification of the hereditary neuropathies. The onset was in the first 5 years of life and there was rather rapid progression so that most patients were almost completely paralysed below the knees and elbows by adolescence. Motor conduction velocities were unmeasurable in five patients because of absent motor responses, but were over 35m/s in all other patients. Five of ten patients tested from the Sydney series have now been shown to have mitofusin
2 (MFN2) gene mutations. Two were compound heterozygotes, that is, recessively inherited; three had dominant (heterozygous) mutations. Another Sydney patient with a less severe phenotype was homozygous for a phe216ser mutation on exon 7 of the MFN2 gene.

In addition to the axonal degenerative forms of CMT listed in Table 25.1, there are several other autosomal recessive axonal polyneuropathies that, for historical or other reasons, have not traditionally been included in CMT classifications. These include severe infantile axonal neuropathy with respiratory failure (now known as SMARD1, see below), giant axonal neuropathy (see the Complex Neuropathies Associated with Central Nervous System Involvement and Metabolic Neuropathies section), and Andermann syndrome, a neuropathy described initially in French Canadians that is associated with agenesis of the corpus callosum and which has been shown to be due to mutations of the gene SLC12A6, encoding the potassium-chloride cotransporter protein KCC3A (Casaubon et al. 1996; Howard et al. 2002).

Pathology of CMT2
The pathology is characterised by the presence of signs of axonal degeneration with secondary involvement of the myelin sheath or Schwann cell. Myelinated fibres, especially those of large calibre, are reduced in number, and regenerative clusters may be seen. Onion bulbs are infrequent. The internodes are shortened and of irregular length on teasing. Acute axonal lesions are rare and the pathological abnormalities may be inconspicuous.

Severe Infantile Axonal Neuropathy with Respiratory Failure
This autosomal recessive axonal neuropathy, that overlaps with spinal muscular atrophy, has been labelled severe infantile axonal neuropathy with respiratory failure (SIANR) (Wilmshurst et al. 2001) or spinal muscular atrophy with respiratory disease (SMARD) (Grohmann et al. 2001) depending on the degree of abnormality in the sensory peripheral nerves.

CMT3/HMSN III OR DEJERINE-SOTTAS DISEASE
The terms CMT3, HMSN type III and Déjerine–Sottas disease are applied to a heterogeneous group of inherited or sporadic neuropathies (Ouvrier et al. 1987) with various ages of onset and severity. The age at onset was widely different in the two patients originally reported by Déjerine and Sottas.

There is no universal agreement as to the limits of this group, and affected patients have been shown to have mutations of genes causing other forms of CMT, but it remains a useful clinical concept. There is considerable genetic heterogeneity, with dominant and/or recessive mutations in PMP22, MPZ, EGR2, GJB1, CNTNAP1 and PRX described. Pathologically, nerve alterations are reminiscent of those in type I but they are more intense. There is a marked decrease of myelinated fibres, especially the larger ones. Onion bulbs are well formed but often consist of double basement membrane lamellae, and the ratio of the axon diameter to the total fibre diameter is higher than normal, indicating hypomyelination. In some cases, there is massive interstitial collagen hypertrophy.

Classic Phenotype
The most typical form (Ouvrier et al. 1987) has an early onset, with slow motor development and hypotonia commonly present during the first year of life. Ambulation is delayed in 30–50% of patients. Weakness is more profound and more diffuse than in type I cases and frequently involves the proximal muscles. Ataxia is consistently present and the weakness may be asymmetrical. Prominent eyes with thickening and eversion of the lips are a not uncommon feature, particularly with PMP22 mutations. Papillary abnormalities and even an Argyll Robertson pupil are occasionally observed. In older patients, tendon reflexes are abolished and nerve hypertrophy is frequent. The course tends to be more severe than in CMT1 and CMT2, but not greatly so, although a few patients are incapable of independent walking by adolescence. Nerve conduction velocities are severely diminished to below 10m/s or cannot be recorded.

Congenital Hypomyelinating Neuropathy
The congenital hypomyelinating neuropathies are usually considered a form of CMT3. Guzzetta et al. (1982) distinguished two groups of congenital cases. A severe form that may resemble Werdnig–Hoffmann disease with congenital hypotonia and paralysis, wasting, respiratory impairment and swallowing difficulties, and may be lethal in a few months or years. A raised cerebrospinal fluid (CSF) protein level is constant, and nerve conduction velocities are unmeasurable or extremely low. Less severe cases exist that permit survival for many years but with severe motor impairment. Some sensory impairment may be observed in the course of such cases.

The pathological picture in most cases is that of marked thinning or complete absence of myelin (amyelinc form or hypomyelinating neuropathy) with formation of onion bulbs containing mainly rings of Schwann cell cytoplasm with little or no myelin. The molecular biological basis of the hypomyelinating cases is poorly defined. The pathological findings have been interpreted as indicating that the process is one of deficient myelin deposition rather than demyelination–remyelination. In some cases, there is proliferation of microfilaments in Schwann cells, along with demyelination (Ulrich et al. 1981). In others, unstable myelin with infolding of myelin lamellae has been described (Peudenier et al. 1993). Cases with congenital arthrogryposis and hypomyelinating neuropathy (Balestrini et al. 1991; Boylan et al. 1992) fall within this group and include Hirschsprung disease.
caused by \textit{SOX10} mutations (Inoue et al. 2002), and the autosomal recessive form of Pelizaeus–Merzbacher-like disease caused by \textit{GJA12} mutations (Uhlenberg et al. 2004). Recessive mutations in \textit{CNTNAP1}, which encodes CASPR, have been described in non-syndromic arthrogryposis multiplex congenita (AMC). Arthrogryposis is not always present and mutations may result in a Déjerine-Sottas phenotype without AMC. Patients showed a marked reduction in motor nerve conduction velocity (<10m/s) and electron microscopy of sciatic nerve shows severe abnormalities of both nodes of Ranvier width and myelinated axons (Laquerriere et al. 2014).

Baets et al. (2011) have recently delineated the genetic basis of early-onset HMSN by testing patients on a panel of 11 common genes. Dominant mutations in \textit{PMP22}, \textit{EGR2}, \textit{NEFL}, \textit{MPZ}, \textit{MFN2}, the CMT1A duplication, and recessive mutations in \textit{FGD4}, \textit{MTMR2}, \textit{MTMR13}, \textit{PRX} and \textit{SH3TC2} were shown to cause a spectrum of disease extending from neonatal hypotonia and breathing and feeding difficulties, to motor delay in the first 12 months of life.

### DOMINANT INTERMEDIATE CMT

Davis et al. (1978) coined the term ‘dominant intermediate’ CMT (CMTDI) for families with median motor conduction velocities in the 25–45m/s range and dominant inheritance. The term has since expanded to include families that have some affected individuals with motor conduction velocities in the CMT1 range and other affected members in the CMT2 range. CMTX1, due to mutations in \textit{GJB1}, also falls within this range, but is classified under X-linked CMT.

CMTDIB is caused by mutations in \textit{DNM2}, the gene encoding the GTPase Dynamin 2. Onset age may vary from early childhood to the fifth decade, and some affected individuals may have rapid progression leading to wheelchair dependence. Some families have proxis, ophthalmoplegia and cataracts (Claeys et al. 2009).

The increased incidence of glomerulosclerosis in patients with CMT has long been identified, and recently, mutations in \textit{JFN2} (inverted formin 2) have been shown to cause CMT with focal segmental glomerulosclerosis leading to end-stage renal failure (Boyer et al. 2011).

### HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

Hereditary neuropathy with liability to pressure palsies (HNPP) is a dominantly inherited disease, rare in childhood, and characterised by an abnormal susceptibility to pressure palsies (Behse et al. 1972) usually with evidence of an underlying generalised neuropathy with moderate slowing of nerve conduction velocities and prolonged distal motor and sensory latencies. In most cases the disease is due to a deletion of the region of chromosome 17 that is duplicated in cases of CMT1A, probably as a result of unequal crossing-over during meiosis (Mariman et al. 1994; Verhalle et al. 1994). Some \textit{PMP22} mutations may cause a similar phenotype. Tyson et al. (1996) reported that the same genetic abnormalities may occasionally be found in cases of multifocal paralysis without pressure sensitivity, thus widening the spectrum of the disease. Affected children may develop symptoms during the first decade, although a later onset is more usual. The paralyses usually involve a single nerve trunk, especially the common peroneal nerve, following prolonged maintenance of postures such as squatting or sitting cross-legged, or the cubital nerve following pressure on the elbow. The brachial plexus, the radial nerve in the spiral groove, and the median nerve at the wrist may also be involved (Li et al. 2002). Paralysis also occurs following a brief, unusual effort such as intense physical activity, especially sport. Many patients develop a carpal tunnel syndrome of early onset, which may be clinically manifested but is present on electrophysiological examination in most cases. A few cases have had evidence of CNS involvement with lesions resembling those of multiple sclerosis on magnetic resonance imaging (MRI) (Sanahuja et al. 2005). Recovery from palsies is usually complete over a period of days to weeks, but in some cases permanent generalised motor and sensory neuropathy eventually develops.

The diagnosis is suggested by the disproportion between the minor degree of trauma and the occurrence of paralysis. The frequent presence of a similar history in relatives is virtually diagnostic. Electrophysiological examination confirms the suspicion of an underlying neuropathy by showing slowed conduction velocities outside the affected territory. Examination of family members may demonstrate a neuropathy even in the absence of attacks. Nerve biopsy, which is not necessary in most cases, can show segmental thickenings of myelin sheaths known as tomacula (Sanahuja et al. 2005). No treatment is known, but avoidance of repeated episodes that may leave sequelae may require changes in lifestyle.

### HEREDITARY NEURALGIC AMYOTROPHY (BRACHIAL PLEXOPATHY)

This is also a dominantly inherited condition, genetically distinct from hereditary neuropathy with liability to pressure palsies. The onset is usually in the second decade, but earlier onset can occur and brachial plexus paralyses at birth may be the first manifestation. Attacks closely resemble those observed in the non-hereditary type of plexopathy. Pain may be intense and precedes weakness usually by a few days.
Weakness persists for variable periods. It is mainly proximal. Recovery takes place over a few weeks to months and is usually complete (van Alfen et al. 2000; Kuhlenbäumer et al. 2005). Occasional patients may experience phrenic nerve involvement or episodes of lumbar plexopathy (Awerbuch et al. 1989; Thomson 1993). In some cases, involvement may be limited to a single branch of the brachial plexus; for example, the long thoracic nerve with isolated palsy of the serratus anterior (Dawkins et al. 2001). The frequency of recurrences is extremely variable (Klein et al. 2002). Around 50% of families with hereditary neuralgic amyotrophy have mutations in the SEPT9 (Septin 9) gene (Kuhlenbäumer et al. 2005). In several families a particular kind of mild dysmorphism with short stature, partial syndactyly of the fingers or toes, characteristic craniofacial features with relatively closely spaced eyes, short palpebral fissures, and epicanthus, and cleft uvula or palate are recognised (Jeannet et al. 2001). The dysmorphism is often related to a specific SEPT9 Arg88Trp mutation. Biopsies of involved nerves may show inflammatory infiltrates and/or acute axonal degeneration (Klein et al. 2002). Treatment is generally symptomatic but prednisolone may result in earlier improvement, especially in pain control (van Alfen et al. 2009).

**THERMOSENSITIVE NEUROPATHY**

Magy et al. (1997) reported on a remarkable family with intermittent episodes of extensive paralysis precipitated by body temperature elevations above 38.5°C with onset in childhood or adolescence, and not allelic to CMT1 or hereditary pressure-sensitive neuropathy. Another patient with HNPP, who developed bilateral peroneal nerve palsies associated with fever, with gradual improvement has recently been described (Pisciotto et al. 2011). It is hypothesised that the raised temperature causes conduction failure by altering the properties of ion channels in the paranode and internode.

**HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES**

The hereditary sensory and autonomic neuropathies (HSAN), also called the hereditary sensory neuropathies, are characterised by sensory (and autonomic) nerve involvement with relative sparing of the motor axons. The loss of pain sensation results in mutilating distal ulcers, delayed wound healing, Charcot joints, osteomyelitis and amputations. The unexplained injuries in young children with sensory neuropathy can simulate child abuse (Makari et al. 1994). Pain insensitivity is not however always caused by a neuropathy, with mutations in the voltage-gated sodium channel genes causing congenital insensitivity to pain and other related phenotypes.

**HSAN1**

*(SENSORY RADICULAR NEUROPATHY)*

HSAN1 differs from all other HSANs in that the symptoms appear late, usually after the first decade, rather than in infancy. The transmission is autosomal dominant. The gene for the classic form, *SPTLC1* (serine palmitoyltransferase long chain subunit 1), is involved in phospholipid biosynthesis and maps to 9q22.1–q22.3 (Dawkins et al. 2001). Symptoms appear in late childhood or adolescence with a progressive loss of sensation in the lower extremities, rapidly complicated by episodes of cellulitis and trophic ulcerations of the feet. Spontaneous stabbing pain may occur. There is loss of pain and temperature sensation with preservation of tactile sensation. Later, all sensation may disappear and the distal upper limbs may become involved. Sensorineural deafness is often present. Peroneal weakness often eventually develops. Motor nerve conduction velocities are mildly slow, and sensory action potentials are absent. The course is slowly progressive. Pathological examination shows a marked reduction in the number of unmyelinated fibres. Small and large myelinated fibres are decreased to a smaller but quite significant extent. The dorsal root ganglia and the spinal dorsal roots supplying the lower limbs are degenerate. Mutations in the gene for subunit 2 of the same enzyme *SPTLC2* on chromosome 14q24 cause a phenotypically similar neuropathy without autonomic signs, designated HSAN1C. The mutations cause an alteration in the substrate specificity of the enzyme, and the accumulation of toxic deoxysphingolipids that are neurotoxic in vitro (Rotthier et al. 2010). An l-serine enriched diet has shown improvement in a mouse model of the disease (Garofalo et al. 2011).

*RAB7* mutations may cause a similar picture or a more typical CMT phenotype (CMT2B). Another similar autosomal dominant entity with later onset and prominent symptoms of gastro-oesophageal reflux and cough has been localised to 3p22–p24 (Kok et al. 2003). HSAN1D is caused by mutations in *ATL1* (Arl function 1) and is characterised by an adult onset of distal sensory axonal neuropathy (Guely et al. 2011). Some patients have upper motor neuron involvement and *ATL1* also causes spastic paraplegia 3A (SPG3A). HSAN1E is caused by mutations in *DNMT1* (DNA methyltransferase 1), and characterised by a sensory neuropathy, dementia and hearing loss (Klein et al. 2011a).

**HSAN2**

*(CONGENITAL SENSORY NEUROPATHY)*

This is an autosomal recessive condition, caused by mutations in the *WNK1* (with-no-lysine K-1) gene, with a congenital or
early onset (Shekarabi et al. 2008). Clinically, most patients have a universal absence of pain sensation resulting in burns and mutilations of the lips or fingertips and in painless fractures, especially of the metatarsals. Tactile sensation is also markedly impaired. Areas of normal sensation are preserved in some patients in whom the limbs and face are predominantly affected. Bladder sensation may be impaired with bladder distension (Verity et al. 1982). Deafness has been described in some patients. In most patients, the disease does not seem progressive or is only very slowly evolving (Ferriere et al. 1992). Motor conduction velocities are preserved but sensory action potentials are unobtainable. Cortical evoked somatosensory potentials were lacking in the lower limbs in some patients. Nerve biopsy often shows grossly atrophic nerves. Myelinated axons are severely reduced in number, but unmyelinated fibres are usually normal or at least not greatly diminished.

**HSAN3 (FAMILIAL DYSAUTONOMIA OR RILEY-DAY SYNDROME)**

HSAN3 is the most common of the sensory and autonomic neuropathies. The disorder is prevalent among Ashkenazi Jews, in whom the disease frequency is between 0.5 and one per 10,000 live births with an estimated carrier frequency of one in 50. Scattered case reports on non-Jewish patients can be found (Guzzetta et al. 1986). The disorder is transmitted as an autosomal recessive trait caused by mutations of the *IKBKAP* (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) gene, which maps to chromosome 9q31 (Slaugenhaupt et al. 2001). Histopathological findings include loss of neurons in the posterior root, Lissauer tract and intermediolateral grey columns (Pearson et al. 1978) and loss of unmyelinated and myelinated fibres in peripheral nerves where catecholamine endings are lacking (Pearson et al. 1974). Substance P-immune reactivity in the substantia gelatinosa of the spinal cord and in the medulla is consistently depleted (Pearson et al. 1982). Sympathetic ganglia are hypoplastic.

Clinical manifestations are mainly referable to the autonomic nervous system. Onset is congenital, and hypotonia, sucking difficulties, a poor cry and vomiting are present from birth. Growth retardation becomes evident later in life. Patients do not have overflow tears. Skin blotching, motor incoordination, unstable temperature and blood pressure, cyclic vomiting and drooling are variably present. Relative indifference to pain is usual (Axelrod et al. 1981). Temperature perception, sweating and cutaneous innervation have been studied by Hilz et al. (2004). Bouts of apnoea and pneumonia are common and are a usual cause of death in infancy and childhood. Oesophageal dilatation and impaired gastric motility are frequent findings. Postural hypotension is almost always present. Scoliosis is a major problem. The gag reflex is often poor. Diagnostic criteria include the absence of fungiform papillae on the tongue, diminished or absent deep tendon reflexes, lack of overflow tears, miosis following instillation of 2.5% metacholine chloride in the eyes and lack of an axon flare after intradermal histamine injection (Axelrod et al. 1974). None of these criteria is individually characteristic, and any of them can be found in other sensory neuropathies. Prenatal diagnosis is possible.

The course of familial dysautonomia is severe; in the early studies in the 1960s only 20% of patients survived to adulthood, although by the 1980s due to improvements in management this proportion had risen to 50% (Axelrod and Abularrage 1982). Digestive and respiratory complications are common and may be aggravated by the frequent occurrence of kyphoscoliosis. Emotional lability with repeated severe breath-holding spells is common. Intelligence remains normal. Treatment is symptomatic. The risk of aspiration pneumonia should be minimised by attention to posture and by meticulous precautions during feeding that may necessitate gavage, gastrostomy or fundoplication. Diazepam is effective in association with chlorpromazine for the treatment of acute crises and of hypertension. The management of scoliosis is difficult and only partial surgical correction of the curve can be achieved in many patients (Kaplan et al. 1997). Families of affected children need considerable psychological support.

**HSAN4 (CONGENITAL INSENSITIVITY TO PAIN WITH ANHYDROSIS)**

This rare disorder is caused by mutations in *NTRK1*, which encodes TrkA, a nerve growth factor receptor. The condition is also known as congenital insensitivity to pain with anhidrosis and is a congenital neuronopathy with episodes of unexplained fever often related to environmental temperature and absence of sweating (anhidrosis). Insensitivity to pain is universal and leads to injuries, self-mutilation and osteomyelitis, especially of the lower extremities. Tongue biting is frequent. Blotching of the skin and pupillary hypersensitivity to metacholine chloride occur (Axelrod and Pearson 1984). Intellectual disability is the rule, measured IQ scores having varied from 41 to 78, the majority being in the sixties (Rosenberg et al. 1994). Motor and sensory nerve conduction velocities are normal or near normal. There is complete absence of unmyelinated and small myelinated nerve fibres in peripheral nerves (Goebel et al. 1980). The Lissauer tract and dorsal spinal roots are also affected.

**HSAN5**

HSAN5 presents as a congenital insensitivity to pain with decreased thermal sensitivity but with preservation of response to tactile and mechanical stimuli and retention of the deep tendon reflexes (Low et al. 1978). It is caused by mutations in the coding region of the *NGFβ* (nerve growth factor beta protein) gene.
receptor) gene (Einarsdottir et al. 2004) that codes for nerve growth factor, the principal ligand for the TrkA receptor. The condition has been described in a single family, and is phenotypically similar to HSAN4, though patients may retain some pain sensation and have normal intelligence. It is characterised pathologically by an almost complete disappearance of small myelinated fibres and a moderate decrease of unmyelinated fibres. Routine motor and sensory nerve conduction studies are normal.

**OTHER FORMS OF HSAN WITH INSENSITIVITY OR INDIFFERENCE TO PAIN**

Several rare and/or controversial types of HSAN have been described. Additional types include HSAN with growth hormone deficiency (Libenfarb et al. 1993), progressive pan-neuropathy with hypotension (Axelrod and Pearson 1984), congenital sensory neuropathy with ichthyosis and anterior chamber syndrome (Quinlivan et al. 1993), deafness, sensory neuropathy and ovarian agenesis (Linsen et al. 1994), and HSAN with cataracts, intellectual disability and skin lesions (Heckmann et al. 1995). HSAN associated with spastic paraplegia is caused by mutations in the CCT5 (cytosolic chaperonin-containing t-complex peptide-1) gene (Bouhouche et al. 2006). The acomitulating sensory neuropathy described in Navajo children, and rarely in other ethnic groups, is a mitochondrial depletion syndrome caused by recessive mutations in MPV17 (Spinazzola et al. 2006). The unexplained injuries in young children with sensory neuropathy can simulate child abuse (Makari et al. 1994).

The term *insensitivity to pain* in principle applies to patients in whom analgesia is the result of abnormalities of peripheral nerves, cutaneous nerve endings or central sensory pathways, whereas *indifference to pain* applies to those who have normal sensory pathways but fail to appreciate the painful nature of stimuli (Manfredi et al. 1981). Such a distinction may well be artificial, and Dyck et al. (1983) have emphasised the fact that precise analysis of cases of indifference to pain shows abnormalities of the peripheral sensory system when sophisticated methods are used. The term ‘congenital insensitivity to pain’ (CIP) is now used to describe all cases with absence of pain perception, irrespective of whether there is an abnormality in the number of myelinated or unmyelinated sensory fibres.

Recently, mutations in a number of genes encoding for sensory nerve ion channels have been shown to cause insensitivity to, or increased perception of pain (Bennett and Woods 2014). Autosomal recessive loss of function mutations in SCN9A, encoding voltage-gated sodium channel Na,1.7; and rarely dominant gain of function mutations in SCN1A (Na,1.9), CIP (Cox et al. 2006; Leipold et al. 2013). CIP is characterised by absence of nociceptive pain all over the body, congenital anosmia (in those with SCN9A mutations) and normal intelligence. Affected children chew their lips, tongue and fingers resulting in disfiguring injuries. Bruises, burns and scalds are common in the first decade. Large fibre sensations including vibration and proprioception remain normal and there is no autonomic dysfunction. Sural nerve biopsies are normal. Inherited erythromelalgia, characterised by episodic pain and erythema of the hands and feet, is caused by dominant gain of function mutations in SCN9A (Yang et al. 2004).

Paroxysmal extreme pain disorder (also known as familial rectal pain) is characterised by severe perineal and rectal, ocular or mandibular pain, often triggered by eating, defecation or emotional factors, and may be associated with other autonomic symptoms. It is caused by dominant gain of function mutations in SCN9A (Fertleman et al. 2006). Gain of function missense variants in SCN9A and SCN10A have been identified in a significant number of individuals with small fibre neuropathy (Faber et al. 2012a, b). Finally, dominant gain of function mutations in TRPA1, which encodes the TRP channel TRPA1, and in SCN11A, have been identified in kindreds with familial episodic pain syndromes (Kremeyer et al. 2010; Zhang et al. 2013). Gabapentin, pregabalin, carbamazepine and mexiletine are currently used for the treatment of chronic pain associated with these ion channel mutations, but have limited efficacy. Specific sodium channel antagonists are in human trials.

The restless legs syndrome, which is a special type of sensory neuropathy frequent in adults, also exists in children (Kotagal and Silber 2004). The related syndrome of periodic limb movements in sleep has its onset before 10 years of age in 20% of cases.

**RECOMMENDATIONS FOR GENETIC TESTING IN CMT**

Classically, CMT and related disorders are classified on the basis of inheritance and nerve conduction tests and this classification is used to direct genetic testing. However, there are now more than 60 genes known to cause CMT and related disorders, and with mutations in the same gene sometimes causing different phenotypes and having different modes of inheritance, identifying the causative gene by traditional Sanger sequencing can be a time consuming and costly process, especially for rarer genetic causes. In specialist neuropathy clinics, around 62–67% of those with CMT will receive a genetic diagnosis (Saporta et al. 2011; Murphy et al. 2012). More than 90% of CMT where the molecular diagnosis is known, is caused by mutations in four genes (*PMP22* including CMT1A caused by the 17p duplication, *GJB1, MPZ* and *MFN2*). The other genes individually make up less than 1% of genetically classified CMT.

There are flowcharts now available that help the clinician prioritise genes for sequencing (Saporta et al. 2011). In CMT1, especially with homogeneously reduced motor conduction velocities, testing for CMT1A should be done initially; this is usually done by MLPA or CGH microarrays. Testing for
the other common genes is then done on basis of nerve conduction findings and inheritance. However, next-generation sequencing technologies including neuropathy-specific panels, whole exome sequencing (WES) and whole genome sequencing (WGS) hold promise as faster and cheaper alternatives. Where appropriate, CMT1A should be excluded prior to the use of these techniques and many next-generation technologies may miss large deletions (though this is expected to change in the near future). It is then recommended that, if available, testing be done on a neuropathy-specific panel, as these are often optimised for complete coverage of the known neuropathy-causing genes. WES and WGS have been used successfully for the identification of novel disease-causing genes and phenotypes, but incomplete coverage of some neuropathy genes could cause disease-causing mutations to be missed in the clinical setting, though this situation is changing rapidly (Rossor et al. 2013).

Once common genetic causes have been excluded, patients should be referred to a specialised neuropathy clinic for assessment and diagnosis. As always, detailed family history, accurate clinical assessment and nerve conduction studies remain cornerstones of diagnosis, as they are often required to select among the many variants identified during next-generation sequencing.

Hereditary neuropathies may constitute a part of more complex neurological diseases involving the CNS (Table 25.2). Friedreich ataxia, a common cause of neuropathy with CNS involvement, is reviewed in Chapter 10.

**HEREDITARY MOTOR AND SENSORY NEUROPATHY WITH CNS INVOLVEMENT**

‘Complicated’ forms of CMT/HMSN have been recognised that are associated with spasticity (HMSN V), optic atrophy (HMSN VI) and retinitis pigmentosa (HMSN VII) (Klein and Dyck 2005). HMSN type V features pyramidal tract signs associated with a motor and sensory neuropathy. This group includes a number of forms of complicated hereditary spastic paraplegia, many of which have an associated axonal neuropathy. Some families with HMSN V have mutations in *MFN2* (Zhu et al. 2005). *KIF5A* mutations also cause a spectrum of disease from spastic paraplegia to CMT2 (Liu et al. 2014). The association of optic atrophy with CMT2, previously designated HMSN VI, is also caused by mutations in *MFN2* (Zuchner et al. 2006). Periventricular white matter change may also be seen with *MFN2* mutations (Chung et al. 2006). Mutations in the mitochondrial gene *MTATP6* are the cause for neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome. Recently, mutations in *MTATP6* have been shown to be a rare cause of genetically undefined CMT2 (Pitceathly et al. 2012). HMSN IV or HMSN with phytic acid excess is Refsum disease.

Polyneuropathy can also be associated with optico-acoustic degeneration as seen with syndromic causes such as CMTX5 (Rosenberg and Chutorian 1967) and riboflavin transporter deficiency as well as with sensorineural deafness in CMT due to mutations in *GJB1, MPZ, PMP2* and *NDRG1* and sometimes with HSAN types I and II (Hamiel et al. 1993; Stojkovic et al. 1999; Kalaydjieva et al. 2000).

Palmar–plantar keratodermia has been described in association with CMT (Tolmie et al. 1988) and with spastic paraplegia (Fitzsimmons et al. 1983; Isidor et al. 2013). The syndrome of cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma is caused by a mutation in *SNAP29* (Sprecher et al. 2005). Wright and Dyck (1995) described early-onset dementia and deafness in association with HSAN I. This has since been shown to be due to *DNMT1* mutations (HSAN1E) (Klein et al. 2011a). Axonal neuropathy associated with juvenile parkinsonism and ophthalmoplegia is on record (van der Wiel and Staal 1981). Patients with *SPG11* mutations, causing autosomal recessive hereditary spastic paraplegia with thin corpus callosum have been described with juvenile parkinsonism and an axonal neuropathy (Anheim et al. 2009). Axonal neuropathy may also be seen during the treatment of parkinsonism with levodopa. Neuropathy, early-onset parkinsonism and ophthalmoplegia may be seen in the mitochondrial depletion syndrome caused by *POLG* mutations. A special form of congenital neuropathy, with associated osseous fragility, intellectual disability and CNS involvement has been reported in one family by Neumann et al. (1976).

**GIANT AXONAL NEUROPATHY**

This condition is characterised pathologically by the presence of massive axonal enlargements filled with neurofilaments. Normal sized axons may be demyelinated and show ‘onion bulb’ structures. The disease probably represents a disorder of cytoplasmic intermediate filament formation affecting both the peripheral and CNS (Treiber-Held et al. 1994). It is transmitted as an autosomal recessive trait. The affected gene, *GAN*, encoding gigaxonin, maps to chromosome 16q24 (Bomont et al. 2000).

The onset is in the first few years of life with motor deficit and areflexia. Progressive deterioration with ataxia, distal weakness and slow dementia ensue. Patients are usually wheelchair-dependent by late adolescence and many die in the third decade. Orthopaedic deformities include scoliosis and deformed feet.
Chapter 25 Disorders of the Peripheral Nerves

Sensory abnormalities are usually present (Ouvrier 1989). Cranial nerves may be involved, and variable intellectual disability is the rule. System degenerations may be associated (Ben Hamida et al. 1990), and diffuse involvement with endocrinological abnormalities has been reported (Takebe et al. 1981).

One remarkable feature is the presence of ‘frizzy’ or ‘woolly’ hair (Treiber-Held et al. 1994), although milder variants, including the not-infrequent cases with absence of the characteristic ‘woolly’ hair have been described (Bruno et al. 2004).

Motor nerve conduction velocities are sometimes slowed and sensory action potentials are often absent. The EEG is often disorganised with increased slow activity and/or spike discharges, and brainstem auditory evoked potentials are altered. On MRI, a high signal from white matter may be present on T2 sequences.

<table>
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**Refsum Disease (HMSN IV)**

**Heredopathia atactica Polyneuritiformis**

Classic Refsum disease is rare in childhood, although some manifestations of the condition may appear early or even be congenital, e.g. bone deformities, especially short metatarsals (Skjeldal et al. 1987). Although Dyck classified Refsum disease as type IV of the HMSN, the condition deserves a special place because of its well-established metabolic disturbance, its remarkable symptomatology and its partially treatable nature. The disease is caused by an abnormal accumulation of phytanic acid (a C16 branched-chain fatty acid) whose beta-oxidation is blocked due to phytanic oxidase deficiency. Most phytanic acid
is of exogenous origin so that reduction of intake, sometimes in association with plasma exchanges (Gibbend et al. 1985; Dickson et al. 1989), results in lowering of abnormally high plasma levels when patients are placed on a phytol-free diet. This treatment is accompanied by increased nerve conduction velocity, return of reflexes, and sensory and motor improvement.

The clinical manifestations of Refsum disease usually begin after 4–7 years of age but are often recognised much later as the progression of the disorder is slow. A few patients have presented in infancy with neurological features (Herbert and Clayton 1994). The picture is one of a chronic but sometimes fluctuating or remittent peripheral neuropathy in which the clinical expression is very variable (Skjeldal et al. 1987). A chronic relapsing picture and even an axonal neuropathy have been reported (Gelot et al. 1995). Ataxia is often marked. Atypical retinitis pigmentosa is present and hemeralopia (night blindness) may be the first symptom. Anosmia, deafness, ichthyosis and disorders of cardiac function are common. Nerve conduction velocities are usually markedly reduced, and plasma level of phytanic acid, which is considerably increased (300–1600µmol/L instead of <10µmol/L). Mutations of the PHYH gene on chromosome 10p13 are responsible. This gene encodes for phytanoyl Co-A hydroxylase. Mutations of a second gene, PEX7, on chromosome 6q22–24 cause a mild form of the disorder (van den Brink et al. 2003).

**OTHER NEUROPATHIES WITH A KNOWN METABOLIC ABNORMALITY**

A number of metabolic diseases feature a neuropathy that may be overshadowed by other neurological or systemic manifestations but may occasionally be the predominant or presenting feature. The main disorders in this group are shown in Table 25.2 and discussed below and in other chapters.

In some cases of metachromatic leukodystrophy, involvement of the peripheral nerves may be the only manifestation for periods of up to several months. Neuropathy with absence of deep tendon reflexes is common in Krabbe disease and has been reported in sialidosis type 1 (Steinman et al. 1980).

Neuropathy due to inherited disorders of porphyria metabolism is very rare in childhood. It can be observed with four diseases: variegate porphyria due to deficiency of protoporphyrinogen oxidase, acute intermittent porphyria due to deficiency of porphobilinogen deaminase, hereditary coproporphyrinuria due to deficient coproporphyrinogen oxidase, and delta-aminolaevulinic aciduria. These diseases are transmitted as autosomal dominant traits with variable penetrance. Prepubertal cases may occur. The symptoms and signs are similar to those in adult patients and are similar in the three types, except for the presence of photosensitivity in variegate porphyria and coproporphyrin. The polyneuropathy can involve both the lower and the upper limbs (Simon and Herkes 2011). The weakness is both proximal and distal and may involve the respiratory muscles. The neuropathy is a predominantly motor axonal neuropathy and sensory involvement is minimal. Acute attacks of colicky abdominal pain, dysautonomic signs such as hypertension, and psychiatric disturbances may be observed. Most cases remain asymptomatic. Bouts of paralysis are often precipitated by administration of drugs, especially barbiturates but also several antibiotics, oral contraceptives, oestrogens, imipramine and methyldopa, among others (Crimlisk 1997). Seizures may be more frequent in children than in adults, and this is of considerable importance as antiepileptic drugs including phenytoin, carbamazepine, ethosuximide and sodium valproate, and also some anaesthetic agents can also trigger attacks. Paraaldehyde and chloral hydrate can be safely used, while gabapentin (Tatum and Zachariah 1995), magnesium sulphate (Sadeh et al. 1991) and levetiracetam (Zaatreh 2005) have also been reported to be safe.

The diagnosis is confirmed by the finding of an increased urinary excretion of porphobilinogen and delta-aminolaevulinic acid. Between attacks, excretion of these compounds may be
absent. Assay of erythrocyte porphobilinogen deaminase is the most accurate way of detecting acute intermittent porphyria, which is often signalled by a red discoloration of urine. Treatment includes prevention of attacks by avoidance of precipitating drugs. During attacks, intravenous haem in the form of haematin or haem arginate (3–4mg/kg/day for 4 days) should be given (Simon and Herkes 2011). Side effects (thrombophlebitis, coagulopathy) are frequent. Haem arginate (Crimlisk 1997) seems both effective and well tolerated. Avoidance of skin trauma and light is important only in variegated porphyria, in which transient polyneuritis is accompanied by increased skin sensitivity.

**Abetalipoproteinaemia (Bassen–Kornzweig disease) or hypobetalipoproteinemia** are autosomal recessive disorders of the synthesis of the beta-lipoprotein due to mutations of the MTTP (microsomal triglyceride transfer protein) or APOB genes respectively (Hooper and Burnett 2014; Lee and Hegele 2014). As a consequence, fat absorption is deficient. Lipids are not transported from the intestinal mucosal cells into the lymphatic system, because beta-lipoproteins are necessary for the formation of chylomicrons. Fat-soluble vitamins are also poorly absorbed, and levels of vitamins A and E in the serum are quite low. Neurological symptoms are the result of the deficit in vitamin E, resulting in peroxidation of the unsaturated myelin phospholipids. Pathologically, there is extensive demyelination of the posterior columns and spinocerebellar tracts, with severe depelement and segmental demyelination of large myelinated fibres in peripheral nerves and posterior roots. Involvement of the anterior horn cells and cerebellar cortex has been reported (Kane and Havel 1995).

The neurological picture is one of spinocerebellar degeneration with progressive ataxia, loss of tendon reflexes, disturbances of deep sensation and pes cavus in association with pigmentary retinal degeneration that gives rise to decreased visual acuity and night blindness. Paralysis of vertical gaze is a frequent feature. Muscle weakness and atrophy may supervene. Indeed, the picture is highly suggestive of a primary spinocerebellar degeneration and it is likely that many cases reported as Friedrich ataxia with retinitis pigmentosa were in fact cases of abetalipoproteinaemia. Neurological manifestations may appear as early as 2 years of age and one-third of patients are symptomatic by 10 years. About the same proportion of patients have intellectual disability. A history of ‘coeliac syndrome’ during the first year of life with foul, bulky stools and abdominal distension is usually obtained, and most children exhibit growth retardation. The diagnosis rests on the presence of retinal lesions with an extinguished electroretinogram, on the finding of low serum cholesterol, triglycerides and vitamin E levels, on the presence of acanthocytosis on blood smears, and ultimately on low or absent apoB levels. The diagnosis can be confirmed on sequencing for MTTP and APOB mutations. EMG may show evidence of denervation, while sensory nerve action potentials and conduction velocities are diminished. Abetalipoproteinaemia is a treatable condition, and is managed with dietary modification and supplementation of fat-soluble vitamins. The dietary fat intake is restricted to less than 30% of total caloric intake, particularly long-chain fatty acids, and medium-chain triglycerides are supplemented. The diet which is also supplemented with high-dose vitamin E (100–300mg/kg/day orally) prevents the development or progression of eye and nervous disease (Kane and Havel 1995; Lee and Hegele 2014). Intramuscular vitamin E is not superior. Administration of vitamin A (200–400IU/kg/day) and vitamin K1 (5mg every 2 weeks) is also advised.

Acanthocytosis is also observed in another dominantly inherited condition, known as **amyotrophic choreoacanthocytosis**, which includes symptoms of basal ganglia dysfunction, peripheral nerve involvement and other neurological features but is observed mostly in adults (Spencer et al. 1987), and in pantothenate kinase-associated neurodegeneration (PKAN)(see Chapter 19).

Vitamin E deficiency may be due, in addition to absence of betalipoproteins, to biliary insufficiency that prevents normal emulsion of fat in the bowel lumen and results in poor absorption, in association with steatorrhoea (Harding et al. 1982; Spencer et al. 1987). A similar result has been observed in a case of intestinal lymphangiectasia (Gutmann et al. 1986). The clinical picture, indistinguishable from that observed with abetalipoproteinaemia, is observed in children with chronic liver disease, especially ductular hypoplasia (Sokol et al. 1985). The condition is amenable to the same therapy as abetalipoproteinaemia.

Rare cases of a similar syndrome **(Ataxia with vitamin E deficiency; AVED; Familial isolated vitamin E deficiency)** mimicking spinocerebellar degeneration have been described in children without liver disease or apparent fat malabsorption (Burck et al. 1981; Harding et al. 1985; Stumpf et al. 1987). For unknown reasons, these patients do not have retinopathy or ophthalmoplegia. This disorder is relatively frequent in Tunisia and results from mutations of the gene encoding the alpha-tocopherol transfer protein (Gotoda et al. 1995; Hentati et al. 1996).

**Tangier disease** is a rare condition characterised by a decrease of high-density lipoproteins and a low cholesterol level. Accumulation of cholesterol esters in Schwann cells produces a sensorimotor neuropathy that may remain subclinical. Two main syndromes are seen: a pseudosyringomyelic syndrome and a multiple mononeuropathy.

Neuropathies are a major manifestation of the various types of amyloidosis but this condition is exceptional before adulthood (Benson 2001).

**MITochondrial Neuropathies**

Mutations in genes responsible for mitochondrial fission, fusion and axonal transport, as with MKN2 and GDAP1 mutations, are known to cause CMT.

Recently, mutations in mitochondrial and nuclear genes encoding mitochondrial function, and usually causing classic multisystemic mitochondrial disease, have been shown to present with or cause predominantly a peripheral neuropathy (Pitceathly et al. 2012; Echaniz-Laguna et al. 2013). A third of
paediatric mitochondrial disease is associated with a peripheral neuropathy, though the prominent CNS manifestations can mask the peripheral nerve dysfunction. However, the clinical and electrophysiological characteristics of the peripheral neuropathy can assist classification of the mitochondrial syndrome and guide genetic testing (Menezes and Ouvrier 2012). POLG mutations cause a sensory ataxic neuropathy, SURF1 mutations cause a demyelinating neuropathy, while pyruvate dehydrogenase deficiency is associated with an axonal sensorimotor neuropathy. Unlike CMT, the neuropathy associated with mitochondrial disease is not length-dependent (Menezes et al. 2016).

A neuropathy is also a frequent feature of the carbohydrate-deficient glycoprotein syndrome (Jaeken and Carchon 1993).

Vitamin deficiencies in association with other poorly defined nutritional factors are a major cause of endemic neuropathy in several developing countries (see Chapter 27).

ACQUIRED DIFFUSE NEUROPATHIES

Acquired neuropathies are most often inflammatory in origin but various toxins and undetermined processes may also cause them. Inflammatory disorders of the peripheral nervous system include two groups of diffuse diseases: the acute polyneuropathies, also termed polyradiculoneuropathies, and the much less common chronic progressive polyneuropathies. Localised inflammatory neuropathies are relatively common, although their mechanisms are poorly known.

ACUTE INFLAMMATORY NEUROPATHY, ACUTE POLYRADICULONEUROTIS, GUILLAIN–BARRÉ SYNDROME AND RELATED DISORDERS

Guillain–Barré syndrome (GBS) is an acute inflammatory disease of peripheral nerves characterised clinically by progressive weakness that usually appears a few days after a viral respiratory or gastrointestinal illness (Yuki and Hartung 2012; Ryan 2013). The nature of the relationship between nerve dysfunction and infection is not completely understood but an immunological mechanism plays an important role. The commonest form is characterised pathologically by acute demyelination, but acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), both due to an acute axonal degenerative process, have been recognised increasingly frequently with a clear peak of incidence in summer, especially in China, Japan, Mexico, Korea and India but also in other countries (van der Meche et al. 1991; Thomas 1992; Feasby et al. 1993).

Pathology

GBS is characterised by the presence of inflammatory lesions scattered throughout the peripheral nervous system from the anterior and posterior roots to distal twigs (Prineas 1981). In the demyelinating variety, the lesions consist of circumscribed areas of myelin loss associated with oedema and the presence of lymphocytes and macrophages. The initial site of lesions is predominantly at the node of Ranvier. Myelin damage is produced mainly by macrophages that penetrate the basement membrane around nerve fibres and strip myelin away from the axon and the body of Schwann cells. Other cases develop vesicular myelin breakdown with the formation of a ‘soap-bubble appearance’ (Hafer-Macko et al. 1996). This appearance is associated with the presence of immunoglobulins and complement on the outside of the associated Schwann cell. In a minority of cases, macrophage-associated demyelination occurs despite a paucity of lymphocytes. These cases may be due to the action of an antibody rather than a T-cell autoimmune process (Honavar et al. 1991). Interruption of the axons with subsequent wallerian degeneration is present only in the most severe cases with intense inflammation. Proliferation of Schwann cells occurs later in the disease, probably as a first step in the remyelination process.

In the axonal forms, AMAN and AMSAN, Wallerian-like degeneration predominates with little evidence of demyelination or lymphocyte infiltration. In AMAN, sensory axons are largely spared. Apart from the axonal degenerative changes, the motor neurons show chromatolysis (Griffin et al. 1995; Visser et al. 1995).

Pathogenesis

The pathological changes seen in the acute inflammatory demyelinating form of GBS (AIDP) resemble those of acute allergic neuritis produced in experimental animals by immunisation with homogenates of peripheral nerves or heterologous myelin as well as by passive transfer of T cells activated to myelin proteins or peptides. In humans, both humoral and cellular factors play a role. Intraneural injection of sera from GBS patients produces demyelination in animals (Feasby et al. 1982). Anti-myelin antibodies have been demonstrated in GBS patients by fixation of the C1 component of complement and are especially high at onset of the disease (Koski et al. 1986). Some antibodies have been found in myelin sheaths and on Schwann cells but no single antigen has been identified in AIDP cases. Activated complement components C3a and C5a have been found in CSF (Hartung et al. 1987). The most attractive hypothesis remains that a pathogenic agent may damage the Schwann cell and myelin, with release of antigens triggering a cascade of events leading to segmental demyelination which, in turn, is responsible for multiple conduction
blocks (Sumner 1981) that are the electrophysiological basis of the clinical manifestations of GBS. Molecular mimicry involving antigens shared between cell wall/capsular lipopolysaccharide or oligosaccharide of antecedent infective organisms and similar targets on the axons is a key element in the axonal forms of GBS. Several *Campylobacter jejuni* serotypes are associated with GBS, particularly Penner type HS/O19.

IgG anti-ganglioside antibodies to GM1, GQ1b, GD1a and GT1a, either as monomers or complexes, are associated with a number of the clinical variants of GBS. High titres of antibodies against gangliosides GM1 and GD1a are found in AMAN and AMSAN, especially when associated with *Campylobacter* infection (Gregson et al. 1993; Vriesendorp et al. 1993). More than 85% of Miller Fisher syndrome cases (see the Clinical Variants of the Guillain–Barré Syndrome and Related Disorders section) have anti-GQ1b antibodies (Yuki et al. 1993). The extracranial nerves, somatic nerve nodes of Ranvier and dorsal root ganglion cells bind anti-GQ1b antibodies, possibly explaining the specificity of the clinical manifestations. These antibodies are also found in AIDP with ophthalmoplegia. Antibodies to GQ1b and GM1 have been shown to block neuromuscular transmission in vitro. Anti-GM1 antibodies interfere with nodal ion channel function (Takigawa et al. 1995). These findings may explain the rapid changes in strength sometimes seen early in the disorder and in response to immunoglobulin therapy.

**Epidemiology**

GBS occurs usually in children over 3–4 years of age but cases of early and even neonatal onset (al-Qudah et al. 1988) are on record. The overall frequency of GBS is 1.9 cases per 100 000 population (Larsen et al. 1985). The incidence was approximately 0.8 per 100 000 per annum in Australian children aged less than 15 years (Morris et al. 2003). The disease usually follows infection or immunisation by 2–4 weeks (Jones 1996). Among the identified infectious agents, a firm connection has been established with CMV, EBV, mycoplasma and *C. jejuni* (Jacobs et al. 1998; Hadden et al. 2001). Poliovirus infection is not a cause (Rantala et al. 1994) although Zika virus is. *C. jejuni* infection, often with diarrhoea, is the most common infection preceding GBS and, even more so, the Miller Fisher variant (Jones 1996). There has been no proven association with poliomyelitis, tetanus or measles immunisation, though a weak association with influenza vaccination has been recently reported, though greatly outweighed by the benefits from immunisation (Haber et al. 2009; Khandaker et al. 2012; Dodd et al. 2013).

**Clinical Features of Guillain–Barré Syndrome**

The onset of GBS is usually fairly rapid with symmetrical bilateral weakness generally affecting the lower limbs. The paralyses then follow an ascending course. Paralysis is generalised in half the cases, predominates in the distal parts of the limbs in 30%, and is rather symmetrical, although minor differences are not uncommon and gross asymmetry has been reported in rare patients (Jones 1996). Predominantly proximal involvement is present in 20% of cases. Neck, back, buttock and leg pain is often prominent at onset, and is important to recognise as an early presenting feature of GBS in young children who may refuse to weight-bear (Roodbol et al. 2011). Paraesthesiae and hypoaesthesiae are present only in a minority of older children.

The facial nerve is involved in approximately 50% of cases, often bilaterally (Hung et al. 1994). In very rare cases, affected children may present with loss of brainstem reflexes, quadriaparesis and respiratory failure, and these severely affected children often have a poorer outcome (Medici et al. 2011). Ophthalmoplegia occurs in 3% of cases (Dehaene et al. 1986). Optic neuritis is uncommon (Behan et al. 1976). Papilloedema may also be associated due to increased intracranial pressure (Morley and Reynolds 1966). Objective evidence of CNS involvement is highly unusual (Willis and Van den Bergh 1988) and certainly uncommon in our experience. Deep tendon reflexes are abolished early in 83% of cases, even in nonparalytic territories (Winer et al. 1988) though preserved or exaggerated reflexes are rarely reported (Yuki et al. 2012). Loss of deep sensation is frequently found at examination later in the illness.

Paralysis of the respiratory muscles is a common complication of GBS and often requires ventilator support (Ropper 1992). Mild respiratory impairment is even more frequent with resulting hypercarbia. In a Sydney study of 71 childhood cases from 1988 to 2004, 21 (30%) had evidence of respiratory involvement but only five required ventilation. Autonomic involvement is present in many patients and may be responsible for hypotension, hypertension, cardiac arrhythmia and even cardiac arrest (Winer et al. 1988). Urinary retention or overflow incontinence may be present in up to 10% of cases. Ataxia, probably of sensory origin, is not uncommon and may dominate the clinical picture. Plantar responses are usually flexor but a Babinski response may be seen (Jones 1996). The CSF is most often normal during the first days of the illness. Elevation of CSF protein appears between 2 and 15 days and reaches a peak by 4–5 weeks after clinical onset. The CSF total protein concentration and the IgG percentage seem to depend mainly on the degree of blood–brain barrier damage, which in turn correlates with the clinical course. Oligoclonal IgG bands are frequently present in the CSF but come essentially from serum. Oligoclonal IgG banding in GBS is transitory and correlates with the development of blood–brain barrier damage, the presence of cranial nerve involvement and the severity of the disease (Segurado et al. 1986). In occasional cases, the CSF protein may remain normal (Sullivan and Reeves 1977). In contrast to protein, cell content of CSF usually remains normal in GBS, the classic albuminoctytocological dissociation, with fewer than 10 cells per mm³. The presence of more than 50 mononuclear leukocytes/mm³ should cast doubt on the diagnosis (Ashby and Cornblath 1990), but a lesser number of cells is acceptable and has no prognostic value.
MRI of the spine is now being increasingly used in the initial assessment of children with suspected GBS. Enhancement after contrast and thickening of the anterior and posterior nerve roots, especially in the thoracolumbar spine and cauda equina are seen in most patients with GBS, though it is not specific for this disease (Mulkey et al. 2010; Yikilmaz et al. 2010; Zuccoli et al. 2011). An MRI is also important to rule out other sinister causes like discitis or transverse myelitis. There are well-established diagnostic criteria for GBS that remain useful in clinical practice (Asbury and Cornblath 1990). New criteria for GBS and MFS, based on results of clinical, EMG and CSF tests, have been proposed, and while these are effective to define cases for research studies, their value in the clinical setting remains to be evaluated (Sejvar et al. 2011).

Electrophysiology

Electrophysiological studies in AIDP (Cornblath et al. 1988; Ropper 1992) show marked slowing of motor conduction velocities, along with prolonged distal latencies consistent with demyelination in about 50% of the patients. Some abnormalities of motor or sensory conduction velocities are present in 90% of patients but, because of the patchy distribution of lesions, the probability of finding abnormalities increases with the number of nerves studied, and the degree of involvement can vary with the nerve studied. In 20% of cases, abnormalities are found in only one or two but not all nerves studied. The amplitude of the sensory action potentials and of the motor action potential is diminished. A conduction block could be demonstrated in at least one nerve in 74% of the cases of Bradshaw and Jones (Bradshaw and Jones 1992). Measurement of F-wave latency may detect abnormalities of proximal nerves or roots that escape routine examination. In AMAN and AMSAN, motor conduction velocities are normal or near normal but the amplitude of the compound muscle action potential is reduced or unmeasurable. In both forms of GBS, the amplitude of the mean compound muscle action potential bears a significant relationship to the prognosis (Cornblath et al. 1988). Signs of denervation and fibrillations indicate greater axonal involvement and may be of poor prognostic significance in adults but are less serious in children (Bradshaw and Jones 1992; Triggs et al. 1992).

Evoked potential studies have shown anomalies of both brainstem auditory evoked potentials and somatosensory evoked potentials (Ropper and Chiappa 1986).

Course of Guillain–Barré Syndrome

The initial phase of gradually increasing involvement lasts 10–30 days. Prolongation beyond 4 weeks suggests a diagnosis of subacute GBS (Hughes et al. 1992; Rodriguez-Casero et al. 2005) or chronic inflammatory polyneuropathy. In some forms (Ropper 1986), paralysis progresses very rapidly with complete quadriplegia in 2–5 days. Such patients often have severe respiratory involvement, and sequelae are more likely than in average cases. A plateau phase then follows. A long plateau phase was found, by some investigators (Billard et al. 1979) but not by others (Winer et al. 1988), to be associated with a relatively poor prognosis and the persistence of motor sequelae. Death is said to occur in 2–3% of childhood cases, although in some adult series (Winer et al. 1988) mortality was as high as 15%, mostly in older adult patients.

Recovery is usually complete. Motor sequelae, often mild, occur in 5–25% of patients. Relapses and late recurrences occur in about 3% of patients (Wijdicks and Ropper 1990). Late recurrences that supervene several years after the first episode probably have a different mechanism from those seen after discontinuation of plasma exchange or corticosteroid therapy and are usually only partial (Ropper et al. 1988). Factors giving an unfavourable prognosis include a rapid development of the paralysis, possibly a long duration of the plateau phase, a marked distal deficit, and the presence of fibrillation potentials and of low amplitude of the mean compound motor unit potentials (Ropper 1986). The prevalent impression that the disease has a better prognosis in children than in adults has been questioned by Kleyweg et al. (1989) and by Jansen et al. (1993) who found no difference in severity between 18 children and 50 adults and therefore recommended that the same treatments should be used in both groups. However, a large collaborative study (Korinthenberg and Monting 1996) confirmed the lesser severity of the disease in children. Rantala et al. (1995) found three major risk factors for more severe cases: onset of symptoms within 8 days of the preceding infection, cranial nerve involvement, and a CSF protein level more than 800mg/L during the first week of the disease.

Treatment of Guillain–Barré Syndrome

Symptomatic treatment is an essential part of the management of GBS. Careful monitoring of vital functions, avoidance of aspiration pneumonia, and tube feeding and respiratory assistance when needed have considerably lessened the mortality rate. Corticosteroid treatment has been shown in controlled studies to have no beneficial effects and even to prolong hospitalisation (Hughes 1991; Hughes et al. 2007). Plasmapheresis and intravenous immunoglobulin (IVIg) have both been shown to shorten the duration of hospital stay and hasten recovery in GBS (Hughes et al. 2012; Raphael et al. 2012). Both therapies are effective when administered within 14 days of symptom onset, though neither has been shown to improve the long-term outcome. Plasmapheresis has been used effectively in children more than 10kg in weight. The demonstration that high-dose (2g/kg) intravenous gammaglobulins (van der Meche and Schmitz 1992; Hartung et al. 1995) is effective opened a new avenue for therapy. Doses of 0.4g/kg per day for 5 days given during the first days of the disease give results similar to those of plasmapheresis (van der Meche and Schmitz 1992). Administration of the total dose in 2 days may be more effective than conventional fractionated therapy (Kanra et al. 1997) but has been
shown to result in more treatment-related relapses in children (Korinthenberg et al. 2005). IVIg infusion has largely replaced plasmapheresis in children because of the ease of administration and fewer side effects. The exact indications for either therapy remain variable: cases with rapid extension or impending respiratory insufficiency are obvious candidates but whether all incipient cases should be treated is often debated. The authors would treat patients who are rapidly evolving or who are non-ambulant on presentation. Rantala et al. (1995) suggested early administration at the time of diagnosis when risk factors are present. A number of ongoing studies (Second IVIg Dose in Guillain–Barre syndrome [SID-GBS] and International-SID-GBS as part of International Guillain–Barre syndrome Outcome Study trial) are evaluating the benefit of a second dose of IVIg on patients with GBS with a poor prognosis (van Doorn 2013).

Differential Diagnosis

GBS is a major cause of acute flaccid paralysis (Table 25.3). The diagnosis of GBS is easy in typical cases. Diagnostic criteria (Asbury and Cornblath 1990) include symmetrical weakness and areflexia, the presence of mild sensory symptoms and signs, progression of the symptoms lasting no more than 4 weeks after onset, absence of fever, sphincter dysfunction and no evidence of CNS involvement.

The conditions that may simulate GBS are common in children (Table 25.3) but only a few raise difficult problems. It is imperative to exclude conditions that require immediate specific treatment, especially spinal cord compression. Transverse myelitis can be distinguished by the finding of a sensory level and sphincter involvement. Rare cases of metabolic disease such as Leigh syndrome (Coker 1993) can closely simulate GBS. Poliomyelitis is now exceptional but some toxic neuropathies may be confused with acute polynu- ritis. In adolescents, the possibility of volatile solvent abuse neuropathy should be kept in mind. Diphtheritic neuropathy closely mimics GBS but is rare. Botulism and diphtheria cause pupillary involvement, which is rarely present in GBS. Tick paralysis can produce a very similar clinical picture but the finding of pupillary paralysis, or of an engorged tick, enables distinction. The clinical and neurophysiological findings are also distinctive (Grattan-Smith et al. 1997) (Table 25.3).

<p>| Table 25.3 Causes of acute flaccid paralysis |</p>
<table>
<thead>
<tr>
<th>Cause</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Peripheral neuropathy</td>
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<tr>
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<tr>
<td>Neuropathies of infectious diseases (diphtheria, neuroborreliosis)</td>
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<td>Acute toxic neuropathies</td>
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<td></td>
<td>Snake (elapid) toxins</td>
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<td></td>
<td>Wild berries, buckthorn</td>
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<tr>
<td>Arthropod bites</td>
<td>Créange et al. (1993)</td>
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<tr>
<td>Anterior horn cell disease</td>
<td>Acute anterior poliomyelitis</td>
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<td></td>
<td>Vaccinal poliomyelitis</td>
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<td></td>
<td>Other neurotropic viruses (cossackie, echoroviruses, enteroviruses 70 and 71)</td>
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<tr>
<td>Acute myelopathy</td>
<td>Cord compression (tumours, trauma, paraspinal abscess)</td>
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<td></td>
<td>Vascular malformation with thrombosis or bleeding</td>
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<td>Demyelinating diseases (multiple sclerosis, Devic syndrome, acute disseminated encephalomyelitis)</td>
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<td>Systemic disease</td>
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<td>Critical illness neuropathy</td>
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<td></td>
<td>Acute myopathy in intensive care patients</td>
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<tr>
<td>Disorders of neuromuscular transmission</td>
<td>Myasthenia gravis</td>
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<td></td>
<td>Botulism</td>
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<td></td>
<td>Insecticide (organophosphate) poisoning</td>
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<td></td>
<td>Tick paralysis</td>
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<td>Snake bites</td>
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<td>Muscle disorders</td>
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<td>Periodic paralyses</td>
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<td>Corticosteroid and blocking agents</td>
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<td>Mitochondrial diseases (infantile type)</td>
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</table>

**CLINICAL VARIANTS OF THE GUILLAIN–BARRÉ SYNDROME AND RELATED DISORDERS**

*Miller-Fisher syndrome* is characterised by the triad of ophthalmoplegia, ataxia and areflexia which comes on rapidly and follows the same illnesses as classic GBS (Kohler et al. 1988; Lin et al. 2012). However, a history or serological evidence of *C. jejuni* infection is particularly common in this syndrome
The nosological situation of the case of childhood peripheral neuropathy with antibodies to P0 myelin glycoprotein (Ben Jelloun-Dellagi et al. 1992) is unclear. Some cases of acute polynuertis cranialis are probably variants of GBS and Miller-Fisher syndrome (Ropper and Chiappa 1986), and the bulk of evidence indicates that Miller-Fisher syndrome is a form of acute polynuertis. The ataxia may be due to involvement of large sensory fibres (Weiss and White 1986). Transitional cases with variable peripheral motor weakness also link the Miller-Fisher syndrome to GBS (Dehaene et al. 1986). The course is similar to that of GBS although recurrences are quite rare (Vincent and Vincent 1986). Cases of sensory loss and areflexia without motor deficit probably represent GBS if the onset is rapid, the distribution widespread and symmetrical, and recovery complete with elevated CSF protein (Dawson et al. 1988). In rare instances, GBS may present mainly with painful manifestations (Mikati and DeLong 1985).

The clinical picture of such cases is highly polymorphic with various combinations of hypotension, disorders of sweating and lacrimation, diarrhoea or intestinal obstruction, pupillary abnormalities and vasomotor disturbances (McLeod and Tuck 1987; Takayama et al. 1987). Acute or subacute cholinergic dysautonomia is characterised by failure of postganglionic cholinergic fibres (including sympathetic efferents to sweat glands), sometimes preceded by a transient increase in function resulting in hypersalivation, increased sweating and more frequent bowel movements. Symptoms include blurred vision, absence of tears, dry mouth, dysphagia, abdominal distension, urinary retention and anhidrosis. Pupils are fixed and dilated, and heart rate is variable. Paralytic ileus may occur. Pure pandysautonomia features in addition symptom and signs of sympathetic failure with resulting postural hypotension, depressed pressor responses and a syncopal tendency. The course is variable, with substantial recovery in some cases. Treatment is symptomatic. Sensory dysfunction may be associated (Nass and Chutorian 1982; Kanda et al. 1990). In some cases, vasomotor dysfunction occurs in isolation; for example, with unilateral flushing (Lance et al. 1988). Dopamine beta-hydroxylase deficiency is a rare cause of similar sympathetic failure (Mathias and Bannister 1992).

In some patients (mostly adults) the course of diffuse inflammatory polyneuropathy is longer than in classic GBS. In particular, the period of progression of the paralysis exceeds 4 weeks and may last up to 8 weeks (Hughes et al. 1992). These patients represent intermediate cases between GBS and the chronic inflammatory neuropathies and may warrant steroid therapy (Rodriguez-Casero et al. 2005).

**CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is much rarer than GBS, with an annual incidence of one per 100,000, but cause up to 10% of cases of chronic childhood polyneuropathy (Ouvrier and Wilmhurst 2003; Rajabally et al. 2009) The diagnostic criteria for CIDP include: (1) a clinical course predominantly of weakness either monophasic, with an initial progressive phase lasting more than 8 weeks, or of a relapsing–remitting nature; (2) electrophysiological and pathological evidence of demyelination; and (3) the absence of systemic disease that may cause demyelinating neuropathy (Ouvrier 1992). Paediatric criteria were proposed by Nevo and Topaloglu (2002). An immunological origin to the condition is likely. There is evidence for both cellular and humoral involvement but molecular mimicry is less clearly involved than in GBS. No definite triggering antigen or pathogenic antibody has been proven to be associated with the disease. There is increased T-cell activation and cytokine release resulting in macrophage-associated peripheral nerve demyelination (Van den Bergh and Rajabally 2013).

**Clinical Features of CIDP**

The disease occurs predominantly in children aged between 5 and 15 years, but cases with infantile or early childhood onset are on record (Sladky et al. 1986; Pearce et al. 2005). Typically, there is a slow subacute onset over at least 2 months of a sensorimotor neuropathy involving the distal and proximal limbs. However, an acute onset as in GBS is possible. Cranial, especially facial, nerve involvement occurs in 10–40% of patients, and weakness of bulbar or respiratory muscles severe enough to necessitate assisted ventilation is present in about 10% of cases (Ouvrier 1992). Because of the usual predominance of weakness in the lower limbs, difficulties with ambulation are usually the first manifestation and in early cases may be responsible for delayed motor milestones. The weakness is not infrequently asymmetrical. It is associated with amyotrophy and sensory disturbances, although these are generally inconspicuous (McCorm et al. 1987; Barohn et al. 1989). Action or postural tremor is present in some patients. In contrast with adults who may have a slowly progressive course, children often have a monophasic disease with improvement, or a relapsing–remitting course (Simmons et al. 1997; Jo et al. 2010).

The CSF shows albumino-cytological dissociation as in GBS in most patients (Ware et al. 2014). The presence of a...
monoclonal or of oligoclonal bands is frequent but the oligoclonal proteins appear to be plasma-derived (Segurado et al. 1986). MRI is now increasingly used to assist with the diagnosis of CIDP. MRI of the spine shows contrast enhancement in the majority of children, with the anterior nerve roots and the cauda equina being most affected. Enlargement of the nerve roots may also be seen (Ware et al. 2014). Similar enhancement may also be seen with inherited neuropathies.

There is consistent electrophysiological evidence of demyelination with slowed motor and sensory conduction velocities, often varying in different segments of the same nerve, increased distal latencies, conduction block, temporal dispersion and abnormal late responses. In contrast, most inherited neuropathies have a homogeneous slowing of motor conduction velocities without temporal dispersion or conduction block. Nerve biopsy (Fig. 25.4) shows endoneurial and sub-perineurial inflammatory oedema and mononuclear cell infiltration. Segmental demyelination and remyelination with less prominent axonal degeneration and fibre loss are seen. ‘Onion bulbs’ are present in about 50% of cases. While a nerve biopsy can provide supportive evidence for a diagnosis of CIDP, the absence of characteristic features, especially after the commencement of steroids does not exclude the diagnosis. The condition is aetiologically related to chronic dysimmune neuropathy (Maisonobe et al. 1996) but gammopathy-related cases are rarely, if ever, seen in childhood.

**Differential Diagnosis**

The main diagnostic difficulty is to distinguish CIDP from inherited neuropathy. Some of the distinctive features of CIDP, like rapid and asymmetrical development of weakness, proximal weakness, conduction block and temporal dispersion on nerve conduction studies and response to immunotherapy, have been documented in a number of inherited neuropathies including CMT1A and due to mutations in GJB1, SH3TC2, Fig4 and SPTLC1 (Ginsberg et al. 2004; Ryan and Jones 2005; Houlden et al. 2006; Houlden et al. 2009; Michell et al. 2009; Cottenie et al. 2013). Metabolic neuropathies, such as metachromatic leukodystrophy, may exhibit similar features with increased CSF protein.

CNS involvement in association with chronic demyelinating neuropathy has been described in some adult patients (Thomas et al. 1987; Ohtake et al. 1990) as well as in childhood (Wäre et al. 2014).

Such cases raise the question of a relationship with multiple sclerosis. Systematic MRI imaging in adult patients with chronic neuropathy has shown the occasional presence of areas of abnormal white matter signal (Feasby et al. 1990). The significance of this finding is unclear.

**Prognosis and Treatment of CIDP**

The disorder does not usually threaten life, but its protracted course and the possible motor sequelae may make it a disabling condition. The prognosis in children is better than in adults and most achieve a full remission (Nevo et al. 1996; Simmons et al. 1997; Ryan et al. 2000; Connolly 2001). Both IVIg and corticosteroids are effective in the treatment of childhood CIDP (Rossignol et al. 2007; Sladky 2008; Teasly 2008). High-dose intravenous immunoglobulin is often the initial therapy of choice because of better side-effect profile, though it is more expensive. The response is often rapid and remission may occur even with only one or two doses of IVIg (2g/kg in total given over 2 or 5 days). Treatment with lower doses is maintained at 3–4 week intervals until a remission occurs or the patient is shown to be a non-responder. Plasma exchange is effective and has fewer side effects than protracted steroid therapy but is difficult in young children.

Therapy with corticosteroids is effective both in children and in adults and may be used if there is no response or only a partial response to IVIg. It is the authors’ practice to commence with 1mg/kg/day of prednisone and to increase to 2mg/kg/day if there is no response. Relapses following minimal decreases in dosage may occur so that prolonged treatment with careful monitoring is sometimes necessary (Wertman et al. 1988). After remission occurs, the steroids are cautiously tapered to minimise side effects. The absence of a response to the first-line agents is rare in childhood, and along with severe side effects, requires an add-on therapy. Immunosuppression with azathioprine, methotrexate, cyclophosphamide, cyclosporine and mycophenolate has been utilised, but no systematic trials are available in children. A favourable response to rituximab has been reported in a small case series (Wäre et al. 2014).

**LEPROSY**

Leprosy is a systemic disease with a marked predilection for superficial nerves, skin, the anterior third of the eye, the upper respiratory tract and the testes. Leprosy is still a major health problem in many resource-poor countries and together with vitamin deficiency is the main cause of neuropathy in many...
regions. The disease is due to infection with *Mycobacterium leprae* and is transmitted by intimate person-to-person contact with only a small proportion of any given population being susceptible. HLA-linked genes control the susceptibility to the organism and the course of the illness. *M. leprae* is the only bacterium to invade peripheral nerves. The unique tropism of *M. leprae* for peripheral nerves (from large nerve trunks to microscopic dermal nerves) and certain immune-mediated reactional states are the major causes of morbidity in leprosy. Hosts with a low resistance to the organism develop lepromatous/multibacillary or nodular infection. Hosts with high resistance develop tuberculoid/paucibacillary infection. The most severe (lepromatous) form of leprosy is twice as common among men than women and is rarely encountered in children.

In lepromatous leprosy, most infiltrates consist of macrophages heavily infected by *M. leprae*. In tuberculoid leprosy, the lesions contain only remnants of bacteria surrounded by well-organised granulomas with epithelioid and giant cells. Borderline cases intermediate between lepromatous and tuberculoid leprosy occur frequently, and unstable cases can oscillate between the two forms. In lepromatous leprosy, neural damage may produce a purely sensory polyneuritis with loss of touch, pain and temperature sensation in a characteristic distribution while deep sensitivity is preserved. Sensory loss first appears in cool areas of the body (ears, dorsal surface of the hands, forearms, feet and lateral aspect of the legs).

Sensorimotor neuropathy is less common (Sabin et al. 2005). Eventually, however, paralysis may develop in the territories of mixed limb and facial nerves. The ulnar nerve is most commonly affected, followed by the peroneal, median, radial, great auricular and other nerves. Hypaesthesia affects fine touch, pain, and heat receptors but generally spares position and vibration sensation. The common involvement of the ulnar nerve at the elbow results in clawing of the fourth and fifth fingers, loss of dorsal interosseous musculature in the affected hand and loss of sensation in the typical ulnar distribution.

Claw hands and also foot drop often develop. Pure mononeuritis is rare. In most patients the onset is insidious but an abrupt onset is possible. Shooting pains are uncommon. Enlargement of peripheral nerves may be present. Its detection is assisted by the use of ultrasonography (Bathala et al. 2012). The diagnosis may be difficult in non-endemic areas. Skin biopsies are helpful and serological tests are available. Nerve biopsy is useful both for diagnosis and for detection of persistent infection (Chimelli et al. 1997). Multi-drug treatment is with dapsone, rifampicin and at times clofazimine. Glucocorticoids are used for the various immune-related reactions which occur in many patients, particularly in the early stages of treatment. Tendon transfers can restore hand and foot function but should not be performed until at least 6 months after the initiation of antimicrobial therapy and the conclusion of episodes of acute neuritis.

### ENDOGENOUS AND EXOGENOUS TOXIC NEUROPATHIES

Toxic neuropathies of both endogenous and exogenous origin are uncommon in childhood at least in symptomatic form (Gamstorp 1968; Evans 1979).

#### ENDOGENOUS TOXIC NEUROPATHIES

**DIABETES MELLITUS**

Subclinical neuropathy may not be rare in patients with juvenile diabetes as judged by electrophysiological findings. Ten per cent of children with chronic diabetes mellitus have symptoms and signs caused by peripheral neuropathy associated with diabetes (Gamstorp et al. 1966). Gallai et al. (1988) found decreased motor conduction velocity in the median nerve in 10%, in the posterior tibial nerve in 32%, and in the sural nerve in 44% of 50 juvenile diabetics with a mean age of 13 years. The neuropathy appeared to be more marked in poorly controlled diabetes. Compared with age-matched control children, impaired vibration perception was present in boys with diabetes in the absence of clinical symptoms of peripheral or autonomic neuropathy (Olsen et al. 1994). Mildly impaired autonomic nervous system function was found in 30–50% of children with diabetes when measured soon after diagnosis (Verrotti et al. 1995; Donaghue et al. 1996). The percentage involved did not change over 3 years (Donaghue et al. 1996). In another large prospective study of nerve conduction and autonomic nervous system function in children with diabetes, slowed sensory nerve conduction velocities and impaired autonomic function were present in 25% of children at the time of diagnosis (Solders et al. 1997). Clinically manifest diabetic neuropathy, however, is rare (Bastron and Thomas 1981; Fiçicioglu et al. 1994), even though the study of spinal sensory evoked potentials also confirms that subclinical involvement of neural transmission in young diabetic patients is common (Cracco et al. 1984). Cranial nerve palsies are exceptional in juvenile diabetes. Autonomic involvement with gastrointestinal features is sometimes apparent. A neurogenic bladder may be relatively common but usually remains asymptomatic (Faerman et al. 1971). Further, asymptomatic children with diabetes have diminished sensation of bladder filling (Barkai and Szabó 1993). Rare cases of mononeuritis multiplex have been recorded (Ouvrier et al. 1999).

**NEUROPATHY OF CHRONIC RENAL FAILURE**

Uraemic neuropathy is also subclinical in a large majority of cases. Seventy-six per cent of affected children had a significant slowing of peroneal nerve conduction velocity without other
Chapter 25 Disorders of the Peripheral Nerves

Evidence of neuropathy in a study by Mentser et al. (1978). Symptomatic patients may experience sensory abnormalities in the lower extremities that may evolve into a sensorimotor polyneuropathy with flaccid paraplegia or quadriplegia. Any type of neuropathy (purely axonal, mixed or predominantly demyelinating) may be observed (Saïd et al. 1983). A purely motor type of uraemic neuropathy (McGonigle et al. 1985) may occur. The neuropathy of uraemia may be related to chronic hyperpolarisation secondary to altered potassium levels (Krishnan and Kiernan 2007) and is usually reversed by successful renal transplant. A case of Miller-Fisher syndrome with a relapsing course and fluctuations temporally related to uraemia and haemodialysis sessions has been observed (Galassi et al. 1990).

**ENDOCRINE NEUROPATHIES**

Polyneuropathy may also occur in hypothyroidism (Nemni et al. 1987) and hypoglycaemia (Mohseni 2001).

**EXOGENOUS TOXIC NEUROPATHIES**

A vast number of chemicals can induce polyneuropathy (Table 25.4). Only the most important ones, especially drugs, are discussed here. Isoniazid can cause a distal mixed sensory and motor neuropathy through interference with the metabolism of pyridoxine. Supplementation with pyridoxine is therefore indicated in patients treated for tuberculosis. Excessive doses of pyridoxine, however, can cause a sensory neuropathy (Schaumburg et al. 1983). Vincristine is a relatively common cause of neuropathy in children with malignancies. The drug interferes with the formation of neurotubules. Abolition of reflexes starting with the ankle jerk is virtually constant following vincristine therapy. In more severe cases paraesthesiae develop, followed by sensory loss then by weakness that may be initially focal and may remain asymmetrical (Casey et al. 1973). Severe pain, in the parotid region, is frequent during vincristine treatment, and oculomotor palsies have been observed. An acute severe deterioration can occur in patients with CMT disease who are given vincristine (Igarashi et al. 1995).

Nitrofurantoin causes neuropathy mainly in children with renal insufficiency. Axonal involvement is the rule, and distal sensory symptoms are usually predominant. Differential diagnosis from uraemic neuropathy may be difficult. The resurgence of thalidomide has resulted in occasional cases of a toxic, mainly sensory, neuropathy in childhood (Fleming et al. 2005).

Most drug-induced neuropathies are reversible after discontinuation of treatment but recovery may be slow, especially when intoxication was prolonged. Phenytoin toxicity is almost always subclinical.

Accidental neuropathies due to heavy metals are rare. Insecticides should be suspected in rural communities, along with arsenic. N-hexane neuropathy may result from solvent abuse (‘glue-sniffing’), a practice that has become prevalent among adolescents and even children (Korobkin et al. 1975). A history of glue-sniffing should be routinely searched for in this

<table>
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<th>Table 25.4 Some exogenous toxic causes of polyneuropathy</th>
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<td>Isoniazid</td>
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<td>Nitrofurantoin</td>
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<td>Complication of bone marrow and solid transplants</td>
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<td>Heavy metals</td>
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<td>Serum sickness</td>
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<td>Arthropod bites</td>
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<td>Tick paralysis</td>
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age group. Nerve biopsy characteristically shows changes of demyelination and giant axons packed with neurofilaments. Gasoline sniffing has also been associated with mononeuritis multiplex (Burns et al. 2001).

Biological toxins are rarely a cause. Most cases of tick paralysis are seen in Australia and the United States. It results in a flaccid, rapidly spreading paralysis involving the respiratory muscles, and may be lethal if the tick is not removed. Careful search is clearly imperative and removal leads to cure in a few hours to several days (Grattan-Smith et al. 1997). In Western Europe, paralysis following tick bite is due to Borrelia disease (see Chapter 11).

NEUROPATHIES OF SYSTEMIC AND VASCULAR DISEASES

A neuropathy may be a manifestation of most vasculitides (see Chapter 12) including lupus erythematosus (McCombe et al. 1987a), rheumatoid arthritis, polyarteritis nodosa, anaphylactoid purpura (Ritter et al. 1983) and other, less well-defined, collagen disorders and vasculitides (Harati and Niakan 1986; Dyck et al. 1987). Such complications are rare in children. They may present as either mononeuritis multiplex or diffuse polyneuropathy (Parikh et al. 1995; Steenlin et al. 1995; Harel et al. 2002). Critical illness neuropathy and myopathy may occur in gravely ill children with multiple organ failure or following major surgery (Heckmatt et al. 1993; Tsao et al. 1995; Williams et al. 2007). They commonly cause generalised weakness and muscle wasting, with failure to wean from mechanical ventilation. There is significant clinical and neurophysiological overlap between the two conditions, such that the term critical illness polyneuropathy and myopathy is often applied. The precise cause of these conditions is obscure. They may entail sepsis, compression, hypoxia (Pfeiffer et al. 1990), toxic and other mechanisms. A similar polyneuropathy can occur in burn patients. Mononeuropathy is often related to electrical or deep thermal burns (Marquez et al. 1993; Kowalske et al. 2001).

LOCALISED DISORDERS OF THE PERIPHERAL NERVES (EXCLUDING CRANIAL NERVES)

INFLAMMATORY LOCALISED NEUROPATHIES

These may involve a single nerve or branch or several nerves as in plexopathies. Transitional forms with the generalised neuropathies exist; for example, neuropathy with liability to pressure palsies or cases of familial brachial plexopathy that may also affect the lumbar plexus and presumably are the result of a more or less diffuse process.

PAINFUL BRACHIAL NEUROPATHY OR PLEXOPATHY, PARSONAGE–TURNER SYNDROME, NEURALGIC AMYOTROPHY

Brachial plexopathy occurs from infancy, although paediatric cases are much rarer than in adults (Charles and Jayam-Truth 1980). It may follow a nonspecific respiratory infection, a specific viral disease such as infectious mononucleosis (Watson and Ashby 1976; Dussaix et al. 1986), parvovirus infection (Denning et al. 1987) or an immunisation (Hamatr-Haddad and Fenichel 1997). In infants, associated osteomyelitis of the humerus must always be excluded. An autosomal dominant form of hereditary neuralgic amyotrophy is due to mutations in the gene SEPT1 encoding septin-9 which is involved in cellular microtubule function (Vassallo et al. 2010; Bai et al. 2013). Rare cases presenting with vocal cord paralysis have been reported in neonates and young children (Leshinsky-Silver et al. 2013).

Neuralgic amyotrophy usually begins with pain localised to the shoulder or involving the whole upper limb. Pain may last from hours to weeks and is often intense. It is followed by weakness which may, however, be the first manifestation in 5% of cases. Paralysis affects the upper brachial roots in over half the patients and the whole plexus in one-third, but may be limited to the hand and fingers in a small proportion. Amyotrophy sets in rapidly and objective sensory signs may be present (England and Sumner 1987). Recovery is virtually constant but it may take months or years and some residua may rarely persist (Zeharia et al. 1990; van Allen and van Engelen 2006).

The diagnosis requires exclusion of spinal cord compression and transverse myelitis, which often demands an imaging study of the brachial plexus and cervical cord. The CSF is usually normal although a mild inflammatory reaction may be present at onset. EMG and nerve conduction studies are useful for determining the extent of involvement of the ipsilateral and, occasionally, the contralateral plexus. Treatment is based on analgesics and physiotherapy. Steroids do not modify the long-term outcome but may have a favourable effect in some cases. Rare cases in childhood may have a different phenotype with only mild or no pain but more extensive paralysis with less recovery than in adults (van Allen et al. 2000; Kotsopoulos et al. 2007). Involvement of only one nerve from the brachial plexus may be seen. The long thoracic nerve is commonly affected with consequent paralysis of the serratus
Chapter 25 Disorders of the Peripheral Nerves

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anterior, producing a unilateral winged scapula. A similar
distribution of weakness, often with less pain but less benign
prognosis, may occur in the Hopkins (asthma-amyotrophy)
syndrome.

OTHER LOCALISED INFLAMMATORY
NERVE DISORDERS

Lumbosacral plexopathy is the counterpart in the lower
limb of neuralgic amyotrophy but is even rarer in children.
Occasional cases are on record in adolescents (Evans et al.
1981) and even in 2–3-year-old children (Sander and Sharp
1981; Thomson 1993). Pain is located in a femoral or sci-
atic distribution and the children will limp or refuse to walk.
Weakness of the leg follows in about a week. Recovery is
almost universal although mild residual weakness may persist.
When the lower plexus is involved, it may be confused with
sciatica due to disc or vertebral disease. In some countries,
schistosomiasis is an important cause of both brachial and
lumbosacral plexopathy (Marra 1983).

Sacral radiculomyelitis (Elsberg syndrome) is observed
mainly in young adults and presents with a tetrad of acute
urinary retention, sensory deficit in sacral dermatomes, par-
aesthesiae in the same territory and pleocytosis of the CSF
(Herbaut et al. 1987). Most cases are due to genital herpes
simplex virus but other viral agents, for example, echovi-
rus and cytomegalovirus, may be the cause (Vanneste et al.
1980; Michaelson et al. 1983; Gerber and Cromie 1996)
(Fig. 25.5).

Figure 25.5 Obstetric paralysis of the brachial plexus. (a) 1-month-old boy with proximal (Duchenne–Erb) palsy. The left arm is internally
rotated, the forearm is extended and pronated. The intrinsic hand muscles are normal. (b) 6-year-old boy with severe sequelae of total plexus
involvement. Synergistic contraction of proximal muscles is evident. The left hand is paralysed and atrophic. There is ipsilateral Horner
syndrome. (Courtesy Dr J-P Padovani, Hôpital des Enfants Malades, Paris.)

(a) (b)

BRACHIAL PLEXUS INJURY

The incidence of brachial plexus injury in neonates has decreased
in recent years probably because of improved obstetric tech-
niques. Since 1980, the incidence varied from 0.37 to 0.87
per 1000 live births (Painter 1988; Evans-Jones et al. 2003).

Two Swedish studies found an incidence of 2.9 and 3.2 cases
respectively per 1000 births (Lagerkvist et al. 2010; Lindqvist
et al. 2012). Women over 35 years of age, those with pre-
eclampsia or diabetes mellitus and those who had previously
delivered children with brachial plexus injuries are more likely
to have affected infants. In one series (Rossi et al. 1982), half of the affected children weighed more than 4000g at birth. Abnormal birth presentations are also a factor but the frequency of breech delivery varies with the series. Occasional cases of prenatal plexus injury due to deformation from uterine constraint, such as that of bicornuate uterus, are on record and are a possible cause of paralysis in siblings (Paradiso et al. 1997).

Pathology
Lesions affect the upper plexus (C5 and C6 roots) – the Duchenne–Erb type of plexus paralysis – in 55–72% of cases; those of C5, C6 and C7 in 10–20%; and those of C8–T1 (Déjerine–Klumpke type) in less than 10%. Lesions of the entire plexus occur on an average in 10% of patients. Bilateral, but often asymmetrical, involvement is not rare. In most instances there is stretching of the upper cord of the plexus due to traction on the shoulder during delivery of the after-coming head or to turning the head away from the shoulder in difficult cephalic presentations. Injury to the lower cord seems to result from traction on the abducted arm during vertex delivery or from traction on the trunk with breech presentation. The most common lesions are haemorrhages and oedema within the nerve sheath of primary plexus cords. Actual avulsion of the roots from the spinal cord with segmental damage of the grey matter or tearing of the nerves is uncommon but occurs when the degree of traction is severe enough.

Clinical Manifestations
In the great majority of patients with upper plexus lesions, the paralysis is recognised from the first days of life. The affected arm hangs limply adducted and internally rotated, the elbow extended, the forearm pronated and the wrist variably flexed (Fig. 25.5). The grasp remains normal. The biceps and brachioradialis reflexes are absent. Weakness of the triceps and extensors of forearm and digits may complicate the picture when there is significant C7 involvement. In lower plexus lesions, intrinsic hand muscles are paralysed, the grasp is absent, and a Horner syndrome with ptosis and miosis is frequently present. If the Horner syndrome does not resolve, the iris fails to pigment and heterochromia iridis develops. Winging of the scapula and Horner syndrome generally herald a poor outcome. In some cases, there is significant sensory involvement with the possible appearance of whitlows on the fingers. Global palsy involving the upper and lower roots of the plexus carries a very poor prognosis for recovery. Involvement of the diaphragm, due to a lesion of the fourth–fifth cervical roots, is present in approximately 5% of cases and may produce symptoms of respiratory distress. This occurs most often in association with upper plexus palsy but may be present in isolation.

Diagnosis
The diagnosis of plexus paralysis is readily apparent. Study of the somatosensory evoked potentials may help distinguish between an avulsed root and a more distal lesion of better prognosis in older patients. MRI of the spinal cord and roots may also be used for the same purpose. EMG may be helpful in determining the extent of paralysis but can be misleading (Yilmaz et al. 1999). Signs of denervation may occur earlier than happens in adults (Swoboda et al. 2003).

Prognosis and Management
A majority of neonates with brachial plexus injury recover (DiTaranto et al. 2004; Strömbeck et al. 2007). This is partly due to the limited nature of the nerve damage but possibly also to the plasticity of the newborn spinal cord (Korak et al. 2004). Gordon et al. (1973) studied 59 such infants: examination showed recovery in 46/52 at 4 months of age, in 48/52 at 12 months, and in 53/56 at 4 years, with only three patients lost to follow-up. Similarly, Greenwald et al. (1984) found that 23 of their 38 patients had recovered by 1 week, 35 by 3 months, and 36 at several years. Children with residual deficits may continue to improve even during preschool years. Sequelae may affect various muscles depending on the lesions but tend to predominate in the proximal limb (Rossi et al. 1982). Sequelae include weakness, atrophy and sensory deficits. Contractures are often more marked than weakness. They are due to faulty re-innervation and result in paradoxical synkinesias. In particular, attempts at any movement of the upper limb tend to provoke contraction of the deltoid and biceps with abduction of the flexed limb. In virtually all cases there is internal rotation of the arm and pronation of the forearm. Subluxation of the humeral head may contribute to the disability (Hernandez and Dias 1988) and require surgery.

The average case of plexus palsy in the newborn infant does not require more than range of motion exercises starting no sooner than 7–10 days after birth. Splinting is contraindicated as it may promote the development of contractures. For infants who have not significantly improved by age 6 months, the question of surgical therapy, including neural lysis, nerve anastomosis or grafting, arises (Gilbert and Tassin 1987; Gilbert et al. 1991). Laurent and Lee (1994) reported satisfactory results in 50 of 70 operated infants, but controversy persists in the absence of a prospective controlled study and no firm statement seems currently possible on the available evidence (Bodensteiner et al. 1994). Surgical intervention after 6–12 months of age is recommended by some groups but the precise indications are not agreed upon (Hunt 1988). Gilbert (2009) has repaired over a thousand infants with brachial plexus injuries who had not recovered biceps function after 3 months and considers that repair is always feasible and that its results are far better than spontaneous progression. In a long-term study, however, Strömbeck et al. (2007) reported that participants undergoing nerve reconstruction had a similar outcome of functional change as the non-operated group. Later orthopaedic surgical procedures on the shoulder appear often to be beneficial.

Postnatal injuries to the brachial plexus are mainly due to motor vehicle (especially motorcycle) and sports accidents.
and consequently affect principally adolescents. The prognosis of these injuries is often guarded. Traumatic lesions of the lumbo-sacral plexus are rare. Both neonatal (Hope et al. 1985) and childhood (Egel et al. 1995) cases have been reported with a favourable outcome.

**SCIATIC NERVE INJURIES**

Injury to the sciatic nerve is now much less often the result of injections into the nerve or its vicinity. Such accidents were particularly prone to occur in small preterm infants because of the small volume of the buttock allowing substances to diffuse right up to the nerve with resulting injury and dysfunction. Therefore, intramuscular injections into the buttocks of such infants are prohibited. The sciatic nerve can also be injured following injection of drugs into the umbilical artery. This is caused by thrombosis of the inferior gluteal artery and is accompanied by circulatory changes in the buttock (San Agustin et al. 1962; Wynne et al. 1978) or gangrenous skin areas in the leg. Similar changes may occur following injection of viscid substances into the buttocks. Paralysis may affect the entire territory of the sciatic nerve or only one of its two main divisions, most commonly the peroneal nerve. Foot drop, amyotrophy and growth disturbances of the leg are the most frequent manifestations. Surgical exploration of the nerve should be considered when no improvement occurs after a few weeks and/or when a granuloma is palpable at the site of injection. The prognosis is poor in severe cases especially as a result of trophic and growth disturbances. Breech delivery is a rare cause of neonatal sciatic palsy (Jones et al. 1988).

Sciatic neuralgia due to disc herniation is rare in childhood, and pain in the territory of the lower lumbar and upper sciatic roots is more common due to tumours than to disc pathology. In children above 10 years of age typical sciatica is occasionally observed. Spinal rigidity and scoliosis or kyphosis may be prominent manifestations (Kurihara and Kataoka 1980; Epstein et al. 1984).

Other causes of sciatic neuropathy in childhood include stretch injury after closed reduction of hip dislocation and due to braces, casts and prolonged abnormal lower extremity postures; compression by haematomas, tumours or lymphomas; and hypersensitivity vasculitis. In rare cases, a localised hypertrophy of the nerve, sometimes due to a perineuroma, or else no evident cause, is found (Jones et al. 1988; Ouvrier and Shield 1999). Perineuromas, occasionally multifocal, occur in other sites including the median and radial nerves (Nagappa et al. 2013).

**CARPAL TUNNEL SYNDROME AND OTHER ENTRAPMENT SYNDROMES**

Carpal tunnel syndrome is rare in childhood; Sainio et al. (1987) collected only 32 published cases and added three of their own. As in adults, the syndrome occurs most commonly in females. Motor symptoms tend to dominate the clinical picture in children with typical involvement of the thenar muscles but the latter can be congenitally hypoplastic (Cavanagh et al. 1979). Pain and paraesthesiae are often less marked than in adults. Sensory and motor distal latencies are prolonged. Mucopolysaccharidoses types I-S, II and IV may cause the carpal tunnel syndrome through mucopolysaccharide accumulation under the flexor retinaculum and related structures. Other rare causes include neuropathy with liability to pressure palsies and the Schwartz–Jampel syndrome (Cruz Martínez et al. 1984). Occasional familial idiopathic cases presenting in childhood are on record (Danta 1975). An infant with suspected congenital insensitivity to pain associated with a family history of carpal tunnel syndrome was completely cured of self-mutilation of his hands by carpal tunnel release (Swoboda et al. 1998).

Other rare entrapment neuropathies of the upper extremities have been reviewed by Dawson (1993) and by Ouvrier and Shield (1999). Entrapment of the sciatic nerve due to a congenital iliac bony abnormality has been reported (Lester and McAlister 1970). Occasional childhood and adolescent cases of the thoracic outlet syndrome due to cervical ribs or fibrous bands are known (Smith and Trojanborg 1987). Radial neuropathies in childhood have been reviewed by Escobar and Jones (1996). MRI helps to diagnose the causes of such cases (Panegyres et al. 1993).

**OTHER TRAUMATIC NERVE INJURIES**

Neonatal injuries to the radial nerve as a result of subcutaneous fat necrosis of the upper arm (Eng et al. 1996) and of the median nerve as a result of attempts at catheterisation of the radial or humeral artery have been reported. Aicardi observed two infants with transient paralysis of the femoral nerve after difficult puncture of the femoral vein and two similar cases following herniorrhaphy and appendectomy. In the latter procedure (for retrocaecal appendicitis), nerve injury was probably due to trauma of the nerve along the psoas muscle. Similar cases are reported in the literature (Stulz and Pfeiffer 1982).

Traumatic palsy of the peroneal nerve may be due to direct penetration or orthopaedic procedures in the region (Jones 1986) and has been reported following infiltration of intravenous fluid (Kreusser and Volpe 1984). Radial paralysis following constraint of the forearm for intravenous infusion is relatively common and always transient.

Lumbar plexus injuries are rare and occur only following major trauma to the pelvis, especially as a result of motor vehicle accidents. Rare cases have been seen following difficult breech delivery (Hope et al. 1985).

Glossopharyngeal neuralgia and hypoglossal nerve paralysis following tonsillectomy have been exceptionally recorded (Ekblom and Westerberg 1966; Sharp et al. 2002). Occipital neuralgia is not rare especially in adolescents (Dugan et al. 1962). The neck–tongue syndrome (Lance and Anthony 1980; Hu and Dougherty 2016) is a headache disorder often
initiated by rapid axial rotation of the neck resulting in unilateral neck and/or occipital pain and transient ipsilateral sensory disturbance in the tongue. It may occur with degenerative or malformative abnormalities of the upper spine, although in many cases the cervical spine appears normal. It is usually treated conservatively with immobilisation in cervical collars, physiotherapy, analgesics and/or local injections. Surgery is not usually required.

Solitary nerve tumours are quite rare in children excepting the benign tumours of neurofibromatosis type I, which usually require no treatment unless they are disfiguring or causing compressive symptoms. Detection of malignant (Triton) nerve tumours is important, however, as effective treatment in many cases the cervical spine appears normal. It is usually treated conservatively with immobilisation in cervical collars, physiotherapy, analgesics and/or local injections. Surgery is not usually required.

Solitary nerve tumours are quite rare in children excepting the benign tumours of neurofibromatosis type I, which usually require no treatment unless they are disfiguring or causing compressive symptoms. Detection of malignant (Triton) nerve tumours is important, however, as effective treatment should not be delayed.

**COMPLEX REGIONAL PAIN SYNDROME TYPE I (REFLEX SYMPATHETIC DYSTROPHY; REFLEX NEUROVASCULAR DYSTROPHY)**

Reflex sympathetic dystrophy, now called complex regional pain syndrome (CRPS) type I, is a syndrome of unknown cause characterised by pain, tenderness, swelling, vasomotor disturbances and dystrophic skin changes typically affecting a single extremity (Schwartzman and McLellan 1987). Three diagnostic criteria have been suggested:

1. Diffuse pain often not localised to anatomical nerve territories and out of proportion to the cause;
2. Loss of function or impaired movements;
3. Some objective evidence of autonomic dysfunction such as skin changes, oedema or osteoporosis.

The disorder follows trauma, usually minor, in 40% of cases and typically occurs in young adolescent girls (Dietz et al. 1990; Gordon 1996). Pain may be so severe as to produce pseudo-paralysis. In children, symptoms tend to be self-limited but a significant minority have protracted and disabling illness. Trophic changes may persist in long-standing cases.

Patients often appear to have a large psychological component to their condition that may also require attention (Bruehl and Carlson 1992). Affected children may have a special psychological profile (Sherry and Weisman 1988) but other authors have denied this (Lynch 1992). Bone scan may help in diagnosing the condition by usually showing localised decrease rather than the increased uptake seen in affected adults. Study by cutaneous thermography of local vasomotor reflex or by monitoring of near-surface blood flow may be of diagnostic value (Gordon 1996). Numerous forms of treatment have been used (Schwartzman and McLellan 1987; Kesler et al. 1988; Dietz et al. 1990) with variable results, including steroids, beta-blockers, calcitonin, vasodilators, transcutaneous nerve stimulation and physiotherapy (Gordon 1996). Infiltration of the regional sympathetic ganglia may be helpful, although involvement of the sympathetic system in the disorder has been contested. Sympathectomy may be used when infiltration proves helpful. A Cochrane Collaboration analysis compared percutaneous radiofrequency thermal lumbar sympathectomy with lumbar sympathetic neurolysis using phenol in 20 participants with CRPS and concluded that sympathectomy should be used cautiously in clinical practice, in carefully selected patients, and probably only after failure of other treatment options (Straube et al. 2013).

Other rare overlapping autonomic disturbances of neural origin include Harlequin syndrome (unilateral diminished sweating and flushing of the face in response to heat or exercise) (Lance et al. 1988). It is sometimes associated with other dysautonomic syndromes such as Horner syndrome, Holmes-Adie syndrome and Ross syndrome (anhydrosis, hyporeflexia, Adie pupil, syncope and other autonomic symptoms (Drummond and Lance 1993), which have been occasionally reported in children (Jain et al. 2013). The cause is often obscure but an adult case due to metastatic deposits has been reported (Guilloton et al. 2013). Beck et al. (1989) reported cases of isolated auriculotemporal syndrome in children, characterised by localised flushing of the face when eating.

**LOCALISED DISORDERS OF CRANIAL NERVES**

The cranial nerves are affected, together with the rest of the peripheral nerves, in many diffuse nerve disorders. Certain conditions more specific to the cranial nerves, whether congenital or acquired, are described in this section (Table 25.5 and Figs 25.6, 25.7 and 25.8). Lesions of the optic, oculomotor and auditory nerves are described in Chapters 22 and 23.

**CONGENITAL FACIAL PARALYSSES**

**Birth Injury to the Facial Nerve**

The facial nerve is the one most commonly involved in birth trauma or prenatal compression. Congenital unilateral facial nerve palsy is observed in approximately 0.3 per 1000 live births (McHugh et al. 1969) but is more common in large infants in whom the incidence is up to 6.5–7.5 per 1000 (Levine et al. 1984). In a majority of cases injury to the nerve is probably the result of pressure on the facial nerve distal to its emergence from the stylomastoid foramen against the sacral prominence of the maternal pelvis. This is suggested by the consistent relationship between fetal position and side of palsy, with left and right palsies observed subsequent to, respectively, left and right occipital positions. Paralysis resulting from application of forceps is comparatively rare. The clinical expression of unilateral facial palsy even when it is complete is not always evident at birth and partial involvement
is not uncommon. In such cases, the orbicularis oculi is most often spared. This is because fibres that course upward just after leaving the foramen are not involved by compression over the parotid gland. When the orbital branches are affected, the palpebral fissure is wider on the affected side and the eye fails to close completely (Fig. 25.6). Finding a periauricular ecchymosis or a haemotympanum helps diagnose traumatic palsy with a likely recovery (Shapiro et al. 1996). In most cases, resolution of the paralysis is observed in a few weeks. Severe injuries with extensive disruption of the nerve seem to be rare. Surgical exploration of the nerve may be considered when no recovery is apparent after 3–6 months.

**Congenital Non-Traumatic Facial Palsy**

Congenital facial palsy can result from various anomalies of the nerve or its nucleus. Lesions of the inner ear may be associated with visible anomalies of the auricle and may be demonstrated by computed tomography (CT) studies showing osseous abnormalities. More often, the nucleus or the nerve itself is abnormal or interrupted (Zucker 1990). Such patients present with unilateral complete paralysis and have no tendency to spontaneous recovery. Electrical stimulation at the stylomastoid foramen in such infants shows no muscle contraction when performed within 48 hours of birth, in contrast to what obtains in traumatic palsy, and is of great value (Shapiro et al. 1996). Surgical exploration of the nerve may be indicated. Congenital facial palsies are also seen in the CHARGE (coloboma, heart defects, atresia choanae [also known as choanal atresia] and Goldenhar) syndromes. Cleidocranial dysostosis and other bony dysplasias of the base of the skull are unusual causes.

**Moebius Syndrome**

Moebius syndrome is characterised by facial diplegia, typically associated with bilateral abducens palsy (Fig. 25.7) and, occasionally, with involvement of several cranial nerves, especially the lower cranial pairs, with frequent tongue involvement (Sudarshan and Goldie 1985). Affectation of the IIIrd nerves is uncommon. The syndrome often results in speech and sometimes feeding difficulties. Intellectual disability is present in about 10–27% of affected children, although the immobile facies, drooling and speech difficulties often wrongly suggest subnormality. Unilateral Moebius syndrome has been reported. The mechanism of Moebius syndrome is probably multiple. A few cases may be of supranuclear origin; most are associated with abnormalities involving the rhombencephalon (Verzijl et al. 2005a) and may be due to absence of the brainstem nucleus (Towfighi et al. 1979).

<table>
<thead>
<tr>
<th>Table 25.5 Facial nerve paralysis: features associated with weakness as a function of lesion location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td>Motor nucleus</td>
</tr>
<tr>
<td>Facial nerve trunk between pons and internal auditory meatus</td>
</tr>
<tr>
<td>Geniculate ganglion</td>
</tr>
<tr>
<td>Facial nerve trunk between geniculate ganglion and emergence of stapedius nerve</td>
</tr>
<tr>
<td>Facial nerve trunk between stapedius nerve and chorda tympani</td>
</tr>
<tr>
<td>Lower facial nerve below chorda tympani</td>
</tr>
</tbody>
</table>

<sup>a</sup>Function subserved by the stapedius nerve.

<sup>b</sup>Function subserved by the greater superficial petrosal nerve (fibres originating from the solitary tract nucleus, coursing through the ganglion).

<sup>c</sup>Function subserved by the chorda tympani (fibres originating from the solitary tract nucleus and joining the facial nerve through its anastomosis with the IXth cranial nerve).
It seems likely that many cases result from prenatal brainstem ischaemia with necrosis and sometimes calcification of the facial nuclei (Thakkar et al. 1977; Govaert et al. 1989; Fujita et al. 1991). Absence or hypoplasia of the facial nerve has been shown pathologically and by MRI studies (Verzijl et al. 2005b). Some cases may be due to congenital muscle aplasia or other muscle disorders (Hanson and Rowland 1971). Numerous cases have been caused by the use of misoprostol as an abortifacient (Marques-Dias et al. 2003). Bavinck and Weaver (1986) have speculated that Moebius syndrome and other regional malformations such as Klippel–Feil syndrome and the Poland anomaly might all be consequences of disrupted blood supply in the territory of the subclavian artery. Hamaguchi et al. (1993) separate three subgroups: children with only cranial nerve involvement, primarily of the VIth and VIIth pairs; patients with associated arthrogryposis; and those with absence or structural deformities of the extremities. The last type comprised 48% of 106 cases collected by Engler et al. (1979), who also encountered absence of the pectoralis major in 9% and micrognathia in 6% of their cases. Rare cases of familial Moebius syndrome are on record (Garcia Erro et al. 1989). In some familial cases, other abnormalities such as Poland anomaly or arthrogryposis may be associated (Gadoth et al. 1979; Sudarshan and Goldie 1985). Genetic studies have not generated consistent involvement of particular genes, except for several case reports implicating the RYRI gene (Shaaban et al. 2013).

**Hypoplasia (or Paralysis) of the Depressor Anguli Oris Muscle**

This is a common minor anomaly (Nelson and Eng 1972). The corner of the mouth on the involved side fails to move downward on crying (Fig. 25.8). The lower lip may be slightly everted on the same side. This anomaly has been thought to be associated with other manifestations, especially congenital heart disease (Levin et al. 1982; Raymond and Holmes 1993), the so-called cardio-facial syndrome. Some are associated with the velo-cardio-facial syndrome of Shprintzen (Puñal et al. 2001). Nevertheless, the vast majority of children with this anomaly do not have other problems and a referral bias is likely.

**Diagnosis of congenital facial palsies**

The major causes of facial weakness are shown in Table 25.6. Congenital palsies represent about 8% of cases of childhood facial paralysis (Manning and Adour 1972), but it is not always easy to distinguish acquired from congenital cases or to separate nerve involvement from weakness due to muscle diseases. Electroneurography may assist in elucidating the causation and prognosis. For all cases with paralysis lasting more than a few weeks without improvement, imaging studies of the base of the brain are indicated. In cases of Moebius syndrome, brain CT and MRI should be performed.
Chapter 25 Disorders of the Peripheral Nerves

ACQUIRED FACIAL PARALYSES

Paralysis of Unknown Cause (Bell Palsy)

Bell palsy is an acute idiopathic paralysis involving the territory of one facial nerve. The pathological changes include considerable oedema but there are few inflammatory signs. The pathogenesis is still uncertain but auto-immune demyelination probably plays a major role. The incidence of Bell palsy is 2.7–4.2 per 100,000 in the first decade of life and 10.1–15.3 per 100,000 in the second decade (Katusik et al. 1986; Drack and Weissert 2013). Both sides of the face are equally involved. Approximately 1–2% of patients have a family history of the disorder. A history of prior viral infection is frequently recorded but its significance is undecided. Multiple viral infections, especially herpes simplex, have been suspected. Neuroborreliosis is a frequent cause in endemic areas (see Paralyses of known cause section). CSF studies in many cases have demonstrated pleocytosis, disordered blood–brain barrier and intrathecal immunoglobulin synthesis (Roberg et al. 1991). There is evidence that Bell palsy may be only the most striking manifestation of an auto-immune disorder affecting other cranial nerves, particularly the sensory trigeminal nerve, which may be involved in up to 50% of cases (Adour et al. 1978; Lapresle et al. 1980).

The first clinical manifestations may be pain or paraesthesiae in the ear or the face unilaterally but these are usually mild or absent. The paralysis reaches its maximum in a few hours and involves all muscles on one side of the face. The face is pulled to the side opposite the paralysis with efforts to use the muscles of expression. The eye cannot be fully closed, and drinking may become difficult. Lacrimation is preserved in many cases but taste sensation is lost in about half the patients (Table 25.5). Weakness remains maximal for 2–4 weeks and then begins to lessen spontaneously (Adour 1982). Complete recovery is the rule in children especially when palsy is partial. Wong (1995) found complete recovery in 21 of 24 children.

When denervation is complete, the onset of improvement may be delayed and recovery may not be total, reaching its maximum within 6 months (Adour 1982). Drack and Weissert (2013) found a full recovery in 89% of children aged 16 years.
and under. Aberrant regeneration with ‘crocodile tears’ or auriculotemporal syndrome (Levin 1987) is exceptional in children. Recurrent paralysis is observed in around 6% of cases (Katusik et al. 1986). Electrical stimulation studies may be useful but are rarely necessary in childhood: incomplete denervation predicts complete recovery, whereas complete denervation may herald the persistence of some weakness. The CSF is abnormal in 10% (Weber et al. 1987) to 75% (Sandstedt et al. 1985) of patients, with increased protein and mononuclear cells, but lumbar puncture is rarely indicated. MRI is not usually indicated but, if performed, demonstrates contrast enhancement most commonly in the distal intra-canicular and labyrinthine segments of the facial nerve (Sartoretti-Scheffer et al. 1994).

The treatment of Bell palsy is purely symptomatic. Protection of an exposed cornea (by lubrication and patching) is essential. Corticosteroids are often advocated for adult patients but they are usually not indicated for children and there is indeed no proof of their efficacy (Burgess et al. 1984; Salinas et al. 2004; Chen and Wong 2005). Since those children who will not recover well usually have a severe paralysis in the early stages, early steroid therapy can be justified in that group. It remains unclear whether antiviral agents are effective (Allen and Dunn 2004).

Paralyses of Known Cause

In endemic areas, facial palsy is frequently the only manifestation of Lyme disease, especially in summer and autumn (Markby 1989; Grundfast et al. 1990). Christen et al. (1993) found that 32.9% of their cases were due to Lyme disease whereas viruses were apparently responsible for 18.4%. Facial palsy in neuroborreliosis may be unilateral; the occurrence of bilateral palsy a few days after involvement of one side is highly suggestive of borreliosis (Keane 1994; Kindstrand 1995). A stiff neck may be found in a quarter of cases. The CSF in such cases consistently shows pleocytosis and increased protein and may contain antibodies against *Borrelia burgdorferi*.

Herpes zoster of the geniculate ganglion (Ramsay Hunt syndrome) is an uncommon cause of facial palsy in children. It may occur without any vesicular rash in the concha (Manning and Adour 1972). Other viruses may cause facial paralysis including Epstein–Barr, chickenpox and mumps viruses. Cases due to Kawasaki disease have been described (Bushara et al. 1997).

Otitis media and mastoiditis, although now uncommon causes, should always be thought of, as antibiotic and/or surgical treatment may be required and as local signs may be extremely subtle. X-rays or CT of the temporal bone are indicated if there is any doubt about the possibility of a local otogenic process.

Tumours, especially rhabdomysarcomas, may compress the nerve and should always be considered.

Hypertension is an infrequent cause of facial palsy (Lloyd et al. 1966) but should be systematically looked for. Recurrent facial palsy may also be due to hypertension as well as to familial Bell palsy (Hageman et al. 1990).

Traumatic paralysis is easy to suspect but demonstration may also require X-ray investigation (May et al. 1981). It may lead to aberrant regeneration and contractures. Facial palsy is also the most common manifestation of neurosarcoïdosis, a rare disorder in children (Scott 1993).

Melkersson–Rosenthal syndrome is characterised by recurrent facial palsy, associated with swelling of the lips, face or eyelids and furrowing of the tongue (Wadlington et al. 1984; Ziem et al. 2000). Facial swelling and palsy may occur in isolation or simultaneously. Often swelling is the initial manifestation. Lingual involvement is inconstant. With repeated attacks, residual paralysis may appear and increase, leading to severe impairment. Histopathological examination reveals noncaseating granulomas on skin biopsy (Elías et al. 2013). Decompression of the facial canal appears to be more effective than steroid therapy (Feng et al. 2014; Tán et al. 2015).

Apart from neuroborreliosis, other causes of bilateral facial palsy in a mixed series of 43 children and adults (Keane 1994) included GBS (six cases), tumours of brainstem or meninges (nine cases), brainstem encephalitis and other miscellaneous causes. Ten cases were idiopathic (bilateral Bell palsy).

Hemifacial spasm-like seizures have been reported in a few infants and children (Al-Shahwan et al. 1994; Arzimanoglou 1996). The onset is usually in the first days of life with repeated attacks of unilateral tonic facial contracture lasting a minute or less and repeated many times daily. The syndrome is regularly associated with a small mass lesion in the cerebellum or in the region of the nucleus of the ipsilateral VIIth nerve that is hamartomatous or neoplastic in nature (Al-Shahwan et al. 1994; Arzimanoglou 1996; Harvey et al. 1996). Harvey et al. (1996) have recorded mass paroxysmal discharges synchronous with the attack that may thus be regarded as a form of subcortical epilepsy. Their patient remained free of attacks following resection of a ganglioglioma. Such attacks differ from true peripheral hemifacial spasm, a rare condition in childhood, which is usually attributed to vascular compression of the VIIth nerve trunk (Ronen et al. 1986). A case presenting in a newborn infant has been reported with a benign course (Zafeiriou et al. 1997).

LOWER CRANIAL NERVE PALSY

Congenital Lower Cranial Nerve Palsies

Impairment of function of lower cranial nerves VII to XII may occur in cases of Chiari I and II malformation (see Chapter 6). Involvement of the abductors of the vocal cords is particularly important as it often gives rise to severe respiratory insufficiency. Some cases are improved by treatment of the accompanying hydrocephalus.

Congenital traumatic laryngeal paralyses are probably related to intrauterine posture with rotation and lateral flexion of the head causing compression of the superior branch
of the laryngeal nerve against the thyroid bone and that of the recurrent nerve against the cricoid cartilage. This produces a dual syndrome of the laryngeal nerve with both disturbances of swallowing due to sensory dysfunction of the superior laryngeal nerve and dysphonia due to involvement of the recurrent nerve (Chapple 1956). The prognosis of such cases is usually good (Narcy et al. 1978). Neurogenic stridor may also be of traumatic origin following forceps delivery or accidental trauma at birth (Maze and Bloch 1979). Other traumatic neonatal paralyses of the lower cranial nerves are uncommon.

Hoarseness due to paralysis of the left recurrent nerve is, in rare cases, a presenting or accompanying symptom of congestive heart failure in infancy or a manifestation of a congenital anomaly of the great vessels of the base of the heart, the cardiovascular syndrome (Condon et al. 1985).

Congenital dysfunction of the vocal cords may occur in isolation and may be genetically transmitted. The posterior cricoarytenoid muscle, which is the sole abductor of the vocal cords and the only laryngeal muscle innervated solely by neurons of the ventral division of the ipsilateral nucleus ambiguus, is affected, resulting in stridor and respiratory impairment. The condition may be familial (Cunningham et al. 1985). The course is towards spontaneous recovery in some cases, while other patients require a tracheostomy to maintain a free airway (Cohen et al. 1982).

Stridor may also be a feature of CNS involvement in infantile Gaucher’s disease and occurs in association with nystagmus in conntal Pelizaeus–Merzbacher disease (see Chapter 10).

In a family with six affected members from three generations with a point mutation in SEPT9, one of the patients presented in the neonatal period with vocal cord paralysis necessitating intubation and prolonged ventilation (Leshinsky-Silver et al. 2013).

Intracranial disorders that produce raised intracranial pressure can be responsible for unilateral or, more commonly, bilateral vocal cord palsy often requiring tracheostomy. Spontaneous regression occurred in four of seven cases reported by Chaten et al. (1991).

Laryngeal nerve palsies may improve significantly following various interventions including thyroplasty, laryngoplasty or re-innervation (Butski et al. 2015).

Congenital dysphagia is rarely due to peripheral nerve involvement and is more often a part of pseudobulbar palsy that may be due to brain malformations or vascular and degenerative disorders. Severe dysarthria is often present in such cases (Van Dongen et al. 1987). Prolonged congenital dysphagia was reported by Mbonda et al. (1995). One of their four patients had associated paralysis of the adductors of the vocal cords. Cine-radiographic study of swallowing showed major difficulties with the pharyngeal stage with only minimal involvement of the first oral stage. Two of the patients died; the others recovered in 20 and 40 months respectively. This syndrome is to be distinguished from benign transient pharyngeal dysfunction observed usually in preterm infants with recovery in a few weeks. EMG of the tongue and pharyngeal muscle confirms the peripheral involvement and helps predict the outcome.

Other Lesions of the Lower Cranial Nerves

A few cases of glossopharyngeal paralysis variably associated with involvement of the Xth and XIth cranial nerves are on record (Greenberg et al. 1987). Glossopharyngeal neuralgia is exceptionally rare in children. Recurrent laryngeal and hypoglossal palsies accompanied by brachial plexus injury or inflammation have also been reported (Haenggeli and Lacourt 1989; Nagappa et al. 2013).

Isolated neuropathies probably related to viral or post-viral diseases may raise serious diagnostic problems in children. Some may affect only one nerve; for example, the hypoglossal nerve (Edin et al. 1976; Wright and Lee 1980), the recurrent nerve (Blau and Kapadia 1972) or the vagus nerve (Berry and Blair 1980). Others may involve both the IXth and Xth nerves, usually on one side, and produce an isolated temporary paralysis of the pharynx that may raise the suspicion of brainstem disease (Aubergé et al. 1979; Roberton and Mellor 1982; Suarez-Zeledon and Brian-Gago 1995). The onset is sudden, often following an upper respiratory infection, more rarely after a specific viral infection such as infectious mononucleosis (Wright and Lee 1980; Sugama et al. 1992; Connelly and De Witt 1994), with nasal reflux and/or dysphagia. Examination shows unilateral paresis of the soft palate and of the posterior pharyngeal wall. Spontaneous recovery occurs in a few days or weeks. Such cases are probably related to post-infectious abducens palsy. XIIth nerve palsy is rare in children (Keane 1996).

MULTIPLE CRANIAL NERVE PARALYSES

As indicated above, multiple involvement of cranial nerves may be more frequent than suspected, and Bell palsy is often the visible part of a subclinical multiple neuropathy. Such multiple nerve involvement in adults may be of vascular origin (Lapresle and Lasjaunias 1986). Affected nerves are few in such cases and belong to a localised arterial territory. In children, multiple cranial neuropathy is more often a manifestation of acute polyneuritis akin to the Guillain–Barré syndrome (Ropper 1986; Waddy et al. 1989). In occasional cases, a known virus is implicated; for example, the varicella-zoster virus (Mayo and Booss 1989).

Idiopathic cranial polyneuropathy is observed mainly in adults (Hokkanen et al. 1978; Juncos and Beal 1987; Uldry and Régli 1988) but may also affect children. Various patterns of multiple cranial nerve involvement can obtain. The most commonly involved nerves are the facial nerves, the oculomotor nerves and the lower cranial nerves, but optic nerve involvement has been reported. The course of multiple cranial neuropathies is often recurrent, and such cases pose differential
diagnostic problems with myasthenia gravis, recurrent facial palsy, the syndrome of Tolosa–Hunt (Sorensen 1988), and some mitochondrial diseases. A migrating course is sometimes observed (Takahashi 1978). The condition may be familial (Sorensen 1988) but little is known about its mechanism. A few cases have been linked to antiganglioside antibodies (Matsubara et al. 1997).

A similar picture may be produced by tumours invading the base of the skull or basal meninges; hence the necessity of a careful radiological examination of such patients. Brain-stem gliomas and encephalitis may also pose a diagnostic problem although they commonly produce signs of long tract involvement. Osseous diseases (hyperostosis cranialis interna) (Manni et al. 1990) may be a rare cause of multiple cranial nerve entrapment.

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- Central Core Disease
- Multiminicore Disease
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Muscle Disorders

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The last few decades have seen an explosion in our understanding of the genetic and pathological basis of neuromuscular conditions, although at this time their treatment remains largely symptomatic.

The genetic and inflammatory myopathies, muscular dystrophies, congenital and acquired myasthenic and neuropathic syndromes of childhood all present with weakness, hypotonia and motor delay. Distinction between these syndromes is based on age at onset, pattern of weakness, associated neurological findings, baseline biochemical and neurophysiological testing. Targeted genetic testing can then be used to confirm diagnosis and guide treatment.

This chapter will describe these conditions in detail and will focus on our current understanding of treatment and management issues in these disorders, looking towards diagnostic and therapeutic challenges for the future.

CONGENITAL MYOPATHIES

Congenital myopathies are characterised clinically by hypotonia and weakness, usually from birth, as well as by characteristic morphological changes on histological and/or electron microscopic examination of muscle. There is wide variation in clinical severity within each form of myopathy and marked clinical overlap with other neuromuscular disorders including the muscular dystrophies, congenital myasthenic syndromes, metabolic myopathies including Pompe disease and spinal muscular atrophy, which can all present in the newborn period with marked hypotonia and weakness (the ‘floppy infant’ syndrome). The differential diagnosis also encompasses other conditions such as Prader-Willi syndrome and neurometabolic disorders in which children may appear profoundly hypotonic without a primary involvement of the skeletal muscles or nerves.

Clinical findings suggestive of congenital myopathies include prominent facial weakness with or without ptosis, a hypotonic (‘frog-leg’) posture with hyporeflexia and weakness of the respiratory and bulbar muscles. The extracocular muscles may be involved in some forms, either at presentation or later in the course of the disorder. Sensation is intact and intelligence usually normal. Histopathological signs of muscle dystrophy are not present, creatine kinase levels are normal or only mildly elevated and the electromyography (EMG) is either normal or myopathic. Muscle ultrasound and magnetic resonance imaging (MRI) are increasingly used to recognise primary myopathies and differentiate between different forms of congenital myopathy. Selective muscle involvement on MRI can be suggestive of a specific disease gene but not all myopathy subtypes have unique MRI signatures. Imaging is usually interpreted in conjunction with the clinical phenotype and results of muscle biopsy, to prioritise or interpret results of gene testing.

Historically, the congenital myopathies have been classified on the basis of the morphological features seen on muscle biopsy – for example, rods (nemaline myopathy), cores (central core disease and multiminicore disease), central nuclei (centronuclear/myotubular myopathy) and selective hypertrophy of type 1 fibres (congenital fibre type disproportion). Over the past 15 years the genetic basis of many of the different forms of congenital myopathy has been identified but it is clear that there are still many additional genes to be discovered. The known genetic causes for the congenital myopathies are summarised in Table 26.1. As demonstrated in the table, the relationship between each congenital myopathy (as defined on histological grounds) and the genetic cause(s) is complex. Many congenital myopathies resulting in an apparently similar muscle pathology phenotype can be caused by mutations in more than one gene (genetic heterogeneity). For example, there are currently ten known genetic loci for nemaline myopathy. In addition, mutations in the same gene can cause different muscle pathologies. Mutations in the ryanodine receptor 1 (RYR1) gene can be autosomal dominant or recessive and may be associated with central core disease, core-rod myopathy, multiminicore disease, centronuclear myopathy and congenital fibre type disproportion. Clinical features can provide valuable clues to help distinguish between different genetic disorders with overlapping pathology (North et al. 2014). The increasing use of next generation sequencing as a diagnostic tool in clinical practice is likely to reduce the need for muscle biopsy as a first-line investigation in the future.
### Table 26.1 Congenital myopathies with identified gene loci

<table>
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<tr>
<th>Inheritance</th>
<th>Protein and gene (symbol)</th>
<th>Notable or specific clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nemaline myopathy (NM)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD, AR</td>
<td>α-tropomyosin\textsubscript{SLOW} (TPM3)</td>
<td>Variable severity, can present in childhood. Foot drop and neck weakness may be prominent</td>
</tr>
<tr>
<td>AD, AR, Sporadic</td>
<td>Skeletal muscle α-actin (ACTA1)</td>
<td>15–25% of NM. Variable severity from severe neonatal to adult onset. Causes 50% of severe lethal NM. Majority have de novo dominant mutations. Rare cases with cardiac involvement</td>
</tr>
<tr>
<td>AD</td>
<td>β-tropomyosin (TPM2)</td>
<td>Foot drop and neck weakness may be prominent. May be associated with distal arthrogryposis, large joint contractures and/or cardiomyopathy</td>
</tr>
<tr>
<td>AR</td>
<td>Nebulin (NEB)</td>
<td>Most common genetic cause of NM (~50%). Typical congenital presentation most common. Lower facial and neck weakness and foot drop may be prominent</td>
</tr>
<tr>
<td>AR</td>
<td>Troponin T1 (TNNT1)</td>
<td>Neonatal onset with hypotonia, contractures and tremors. Progressive weakness, severe pectus carinatum and early childhood death may occur due to respiratory insufficiency. First reported in Amish</td>
</tr>
<tr>
<td>AR</td>
<td>Cofilin (CFL2)</td>
<td>Only two families reported. No facial weakness or foot drop</td>
</tr>
<tr>
<td>AD</td>
<td>Kelch repeat and BTB domain 13 containing (KBTBD13)</td>
<td>Childhood onset, proximal weakness with ‘slowness’ of muscle movements. Facial, cardiac and respiratory muscles spared</td>
</tr>
<tr>
<td>AR</td>
<td>Kelch-like family member 40 (KLHL40)</td>
<td>Severe congenital, lethal. Fetal akinesia, respiratory and bulbar weakness</td>
</tr>
<tr>
<td>AR</td>
<td>Kelch-like family member 41 (KLHL41)</td>
<td>Five families reported to date. Variable severity from neonatal lethal to intermediate or typical forms of NM</td>
</tr>
<tr>
<td>AR</td>
<td>Leiomodin 3 (LMOD3)</td>
<td>Usually severe congenital lethal, occasional typical congenital. 30% extraocular muscle involvement. Marked facial weakness, respiratory and bulbar involvement</td>
</tr>
</tbody>
</table>

**Cap disease (NM variant)**

| AD | β-tropomyosin (TPM2) | Most common cause of cap disease. As for NM due to TPM2 |
| AD | α-tropomyosin\textsubscript{SLOW} (TPM3) | As for NM due to TPM3 |
| AD | Skeletal muscle α-actin (ACTA1) | Single case reported to date |

**Zebra body myopathy (NM variant)**

| AD | Skeletal muscle α-actin (ACTA1) | As for NM due to ACTA1 — single case reported to date |

**Core-rod myopathy (overlap of NM and CCD)**

| AR | Nebulin (NEB) | One case reported to date. Severe neonatal presentation requiring ventilatory support. Multiple joint contractures and scoliosis |
| AD, AR | Ryanodine receptor (RYR1) | As for core myopathies (below) |
| AD | Kelch repeat and BTB domain 13 containing (KBTBD13) | As for NM due to KBTBD13 |

**Central core disease (CCD)**

| AD | Ryanodine receptor (RYR1) | Almost all cases of AD CCD. Mild-moderate weakness sparing the respiratory, bulbar and extraocular muscles. Contractures, congenital hip dysplasia and skeletal deformity may be prominent. High risk of malignant hyperthermia. Characteristic pattern of muscle involvement on MRI |

**Multiminicore disease**

| AD, AR | Ryanodine receptor (RYR1) | Wide range of muscle weakness from mild to severe. AR cases tend to be more severe. May be associated with external ophthalmoplegia, ptosis, respiratory and bulbar involvement and contractures |
| AR | Selenoprotein N (SEPN1) | Congenital axial weakness with head drop. Most develop respiratory failure and scoliosis by late childhood/early teens with relatively preserved limb strength |
| AD | Skeletal muscle α-actin (ACTA1) | Rare – single case report to date |
| AR | Titin (TTN) | Progressive myopathy and severe cardiomyopathy |

*Continued*
There are currently no curative treatments for the congenital myopathies but a multidisciplinary approach to the management of affected individuals can greatly improve both quality of life and longevity, in particular physical and occupational therapy, orthopaedic intervention, anticipatory respiratory care and management of feeding difficulties. While progression of muscle weakness is usually only very slow or even absent, some complications (scoliosis; respiratory insufficiency) are very common in congenital myopathies and if untreated can lead to death. In severely affected infants survival into childhood can be very challenging. Prenatal diagnosis is available for many of these disorders once their genetic cause is identified.

### NEMALINE MYOPATHY

The ‘typical congenital’ form of nemaline myopathy usually presents at birth or during the first year of life with hypotonia, weakness and feeding difficulties. Some children present later with delayed motor milestones, a waddling gait or speech abnormalities however occasionally some will not present till adulthood. Facial weakness is common while there is often distal as well as proximal weakness, which may be a clue to genetic subtype. The respiratory muscles are always involved and hypoventilation may be subclinical; many children require active ventilatory support. Cardiac involvement is rare with muscle weakness often static or only very slowly progressive: most patients are able to lead an active life.

The ‘severe congenital’ form of nemaline myopathy presents at birth with severe hypotonia and muscle weakness, fetal akinesia and little spontaneous movement postnatally, difficulties with sucking and swallowing and respiratory insufficiency. Death due to respiratory insufficiency or recurrent pneumonia is common during the first weeks or months of life although occasional patients survive and achieve the ability to walk (Ryan et al. 2001).

The diagnostic feature of nemaline myopathy is the presence of distinct rod-like inclusions – nemaline bodies – in skeletal muscle fibres. Rods are not visible on haematoxylin and eosin (H&E) staining but appear as red or purple structures against the blue-green myofibrillar background with the modified Gomori trichrome stain and are derived from the lateral expansion of the Z-line. Additional pathological features of nemaline myopathy include type I fibre predominance, fibre atrophy and/or fibre hypertrophy (Ryan et al. 2003).

### Table 26.1 Congenital myopathies with identified gene loci (continued)

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Protein and gene (symbol)</th>
<th>Notable or specific clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked</td>
<td>Myotubularin (MTM1)</td>
<td>Also known as myotubular myopathy. Severe congenital onset in males, bilateral ptosis, facial weakness and limitation of eye movements. Birth length often &gt;90th centile, macrocephaly, narrow elongated face and slender long digits</td>
</tr>
<tr>
<td>AD</td>
<td>Dynamin 2 (DNM2)</td>
<td>Variable severity from congenital to adult-onset. Relative weakness of neck flexors, external ophthalmoplegia and ptosis, facial weakness. Characteristic pattern of involvement on MRI</td>
</tr>
<tr>
<td>AR</td>
<td>Amphipysin 2 (BIN1)</td>
<td>Few cases reported to date</td>
</tr>
<tr>
<td>AR</td>
<td>Ryanodine receptor (RYRI)</td>
<td>As for AR multiminicore myopathy</td>
</tr>
<tr>
<td>AD</td>
<td>Skeletal muscle α-actin (ACTA1)</td>
<td>As for NM due to ACTA1. Uncommon, more likely in patients with severe weakness</td>
</tr>
<tr>
<td>AD</td>
<td>α-tropomyosin, SLOW (TPM3)</td>
<td>25–50% of cases of CFTD. As for NM due to TPM3. Most patients ambulant in adulthood</td>
</tr>
<tr>
<td>AR</td>
<td>Ryanodine receptor (RYRI)</td>
<td>20% of patients with CFTD. Weakness often severe. As for multiminicore disease due to RYRI</td>
</tr>
<tr>
<td>AD</td>
<td>β-tropomyosin (TPM2)</td>
<td>Rare. As for NM due to TPM2</td>
</tr>
<tr>
<td>AR</td>
<td>Selenoprotein N (SEPN1)</td>
<td>As for multiminicore disease due to SEPN1</td>
</tr>
<tr>
<td>X-linked</td>
<td>Linked to Xp22.12–Xq22.1</td>
<td>Males – severely usually lethal congenital onset weakness with ptosis, facial weakness and respiratory weakness. Female carriers – variable facial weakness with ptosis</td>
</tr>
<tr>
<td>AD</td>
<td>Slow myosin heavy chain (MYH7)</td>
<td>Scapuloperoneal or limb-girdle weakness. Foot drop, calf hypertrophy, scoliosis and respiratory muscle weakness. May be associated with cardiomyopathy</td>
</tr>
</tbody>
</table>

Adapted from North et al. (2014).

AD, autosomal dominant; AR, autosomal recessive.
new dominant mutations). To date, disease-causing mutations have been identified in ten genes (reviewed in Romero et al. 2013; North et al. 2014). Seven of these genes encode protein components of the thin filament of muscle: α-tropomyosin (TM), nebulin, skeletal α-actin, β-tropomyosin, troponin T, coflin and leiomodin 3 (Table 26.1). Three genes (KBTBD13, KLHL40, KLHL41) are likely to be involved in regulating the turnover or breakdown of proteins in the sarcomere although their exact function is as yet unknown. Recessive mutations in nebulin are likely to account for up to 50% of individuals affected by nemaline myopathy. Sporadic or new dominant mutations in the skeletal α-actin gene (ACTA1) account for 20–25% of individuals (and up to 50% of newborn lethal presentations). The other genes are relatively rare causes of nemaline myopathy and there are further genes to be identified.

CENTRAL CORE DISEASE

Central core disease (CCD) usually presents in infancy with weakness, hypotonia and poor muscle bulk, primarily affecting the proximal musculature and lower extremities. Most affected individuals achieve ambulation but motor milestones are typically delayed and muscle weakness generally static or only slowly progressive. There may be mild facial and neck muscle weakness and extraocular muscles are usually spared. Musculoskeletal deformities such as kyphoscoliosis, congenital hip dislocation, pes cavus, pes planus and thoracic deformities occur frequently. Significant respiratory insufficiency is unusual, cardiac abnormalities are not part of the condition and intellectual performance is not impaired (Shuaib et al. 1987). Although most patients display the ‘typical’ clinical phenotype, central cores on muscle biopsies may be found in children who are asymptomatic and have isolated hyper-CK-emia as well as in patients with mild weakness or skeletal deformity (Shuaib et al. 1987; Quinlivan et al. 2003). At the other end of the spectrum severe and fatal infantile variants have also been described.

The characteristic pathological abnormality of CCD is the presence of central cores: central single, well-circumscribed circular regions in the majority of type 1 fibres which represent zones of reduced oxidative enzyme activity staining negatively for phosphorylase and glycogen (Quinlivan et al. 2003). Cores are devoid of mitochondria and sarcoplasmic reticulum (Quinlivan et al. 2003). In most individuals there is type 1 fibre predominance, and type 1 fibres are typically smaller than type 2.

Central core disease has traditionally been regarded as an autosomal dominant disease with variable penetrance. De novo mutations are relatively common. Recessive inheritance is now also recognised, particularly when individuals are affected severely (Ferreiro et al. 2002; Romero et al. 2003). Where histological changes and clinical features are typical of CCD, most patients have dominant changes in the ryanodine receptor gene (RYR1) (Wu et al. 2006), but there is significant clinical and pathological overlap with other variants of RYR1-related myopathy, including the fact that ‘typical’ pathological changes can evolve with time in the same patient from multiminicore to central core so that these group of conditions are increasingly referred to as ‘RYR1-related core myopathies’. The RYR1 gene encodes the skeletal muscle ryanodine receptor 1 which allows release of calcium from the sarcoplasmic reticulum into the sarcoplasm, triggering muscle contraction. CCD is allelic to malignant hyperthermia susceptibility, hence anaesthetic precautions are essential in all patients and in anybody with undiagnosed muscle weakness with possible autosomal dominant inheritance. Some patients with malignant hyperthermia susceptibility have cores on muscle biopsy and mutations in RYR1, despite having normal muscle strength.

The clinical spectrum of RYR1-related myopathies has recently been expanded with identification of children with dominant or recessive core myopathies (CCD or multiminicore disease) presenting with arthrogryposis, severe weakness and respiratory failure in the neonatal period (Romero et al. 2003); see Multiminicore Disease section below. Ophthalmoplegia and ptosis are present in some affected children who may require ventilatory support from birth, however surviving children can demonstrate considerable improvement in respiratory and peripheral muscle strength with increasing age.

MULTIMINICORE DISEASE

Multiminicore disease is a clinically and genetically heterogeneous disorder. Two main forms are recognised, one characterised mainly by rigidity of the spine and early respiratory insufficiency (RSMD1) with the other allelic to CCD, caused by recessive mutations in RYR1 and often associated with ophthalmoplegia.

The rigid spine syndrome phenotype of multiminicore disease is caused by recessive mutations in the gene for selenoprotein N (SEPN1), presenting in the first year of life. Affected infants are hypotonic and weak, with joint hyperextensibility and delayed motor development. Weakness is predominantly axial; the neck flexors are usually the most affected muscles, resulting in poor or absent head control in infancy. Facial weakness is common and the extraocular muscles are spared: intelligence is normal. Kyphoscoliosis and spinal rigidity are common and can progress rapidly during periods of rapid skeletal growth, particularly adolescence (Ferreiro et al. 2000; Jungbluth et al. 2000). This is almost invariably associated with progressive respiratory insufficiency (Ferreiro et al. 2000; Jungbluth et al. 2000). Most patients develop respiratory insufficiency in late adolescence or early adulthood (Ferreiro et al. 2000) although most remain independently ambulant.

Recessively inherited RYR1-related core myopathies with multiminicores show a similar distribution of weakness and wasting but additional extraocular muscle involvement, most pronounced on abduction and upward gaze (Ferreiro et al. 2000). Respiratory impairment is usually milder than in the classic form although bulbar involvement may be pronounced. This variant is far more common than the SEPN1–associated RSMD1 (Maggi et al. 2013).
Minicores are seen as multiple focal defects in oxidative enzyme activity in the majority of muscle fibres on histochemical preparations; they occur in both type I and type II fibres (Ferreiro et al. 2000; Jungbluth et al. 2000). Associated features include increased fibre-size variability, central nuclei, hypotrophy of type I fibres and type I fibre predominance (Jungbluth et al. 2000).

Other genes are also rarely associated with core myopathies (both central and multiminicores): in individuals with associated cardiomyopathy mutations in MYH7 (Cullup et al. 2012) and titin (TTN) (Carmignac et al. 2007) should be considered.

Core-rod disease is characterised by the presence of both central cores and nemaline bodies on muscle biopsy; these may be in the same or separate muscle fibres. The most common cause of true core-rod myopathy is mutations in the RYR1 gene; both dominant and recessive mutations have been described (Scacheri et al. 2000; Ferreiro et al. 2002). Nebulin mutations are an uncommon cause of recessive core-rod disease (Romero et al. 2009).

CENTRONUCLEAR MYOPATHIES

There are three groups of centronuclear myopathies (CNMs) based on clinical and genetic features. The X-linked recessive form (also known as myotubular myopathy) usually has onset in utero and the pregnancy is complicated by polyhydramnios. Affected males present at birth with severe floppiness and weakness, facial diplegia, and difficulties with respiration and feeding. Additional features include thin ribs, contractures of the hips and knees, ophthalmoplegia and cryptorchidism. Many affected boys die in the neonatal period, but a minority survives longer, often requiring permanent respiratory support (McEntagart et al. 2002). The gene for X-linked myotubular myopathy, MTM1 (Laporte et al. 1996), is thought to be involved in a signal transduction pathway necessary both for late myogenesis and excitation-contraction coupling. The characteristic histological feature is predominance of small type 1 fibres with centrally placed nuclei that occupy a large volume of the fibre, resembling fetal myotubes. The major differential diagnosis, congenital myotonic dystrophy, must be excluded by genetic testing. Obligate carriers of the X-linked form of myotubular myopathy are usually asymptomatic but as many as 50% have changes on muscle biopsy. Manifesting carriers may have skewed X-inactivation and more severe weakness on a rare basis.

The autosomal dominant form of CNM due to mutations in the gene encoding dynamin 2 (DNM2) has a wide range in severity from congenital- to adult-onset weakness (Bitoun et al. 2005). Features suggesting this diagnosis include relative weakness of neck flexors, facial weakness, external ophthalmoplegia and ptosis. De novo mutations are relatively common, particularly in patients with severe phenotypes. Centralised nuclei and strands radiating from the centre of the fibre (radial sarcoplasmic strands) on the oxidative stains are characteristic findings on muscle biopsy in DNM2- and BIN1-related CNM, although they may be less apparent in younger children (Romero 2010).

Ryanodine receptor (RYR1) mutations are another cause of autosomal recessive centronuclear myopathy presenting in infancy or early childhood with respiratory distress, hypotonia, a weak cry and difficulty sucking (Romero 2010). Ophthalmoplegia, ptosis and facial diplegia are common. The clinical course is characterised by delayed motor milestones, slowly progressive weakness as well as development of contractures and scoliosis. Amphiphysin 2 (BIN1) mutations also cause a rare variant of autosomal recessive centronuclear myopathy (Nicot et al. 2007). Recessive mutations in the SPEG gene have recently been shown to cause a centronuclear myopathy with dilated cardiomyopathy (Agrawal et al. 2014).

CONGENITAL FIBRE-TYPE DISPROPORTION

Fibre-size disproportion occurs as a secondary phenomenon in a wide range of skeletal and neuromuscular conditions including CNS disorders, peripheral neuropathy, muscular dystrophy and other congenital myopathies such as nemaline myopathy, multiminicore disease and centronuclear myopathy. Congenital fibre-type disproportion (CFTD) is a diagnosis of exclusion, which is best reserved for patients who have clinical features of a congenital myopathy with reduction in type 1 (slow twitch) fibre size relative to type 2 (fast twitch) fibres (at least 35–40%) as their only significant histological abnormality (Clarke and North 2003).

CFTD is genetically heterogeneous and may be associated with autosomal dominant or recessive inheritance. De novo dominant mutations have been identified in skeletal α-actin (ACTA1), α-tropomyosin SLOW (TPM3) and β-tropomyosin (TPM2), all of which are also associated with nemaline myopathy (Table 26.1) (Laing et al. 2004; Clarke et al. 2008; Brandis et al. 2008). Recessive mutations have been identified in the gene encoding selenoprotein N (SEPNT1) (Clarke et al. 2006) and the ryanodine receptor (RYR1) (Clarke et al. 2010). The clinical presentation is variable depending on the genetic subtype (Table 26.1).

CONGENITAL MUSCULAR DYSTROPHIES

The term congenital muscular dystrophy (CMD) applies to children with hypotonia and weakness identified in the first 2 years of life – often from birth – with dystrophic abnormalities on muscle biopsy. Affected children often have congenital joint contractures and may have involvement of the central nervous system, most often involving the brain and/or eyes. The serum creatine kinase is elevated- sometimes markedly so – in most forms of CMD. Weakness is usually slowly
progressive although some children have an essentially static course (Bonnemann et al. 2014).

In recent years the number of identified discrete clinical and genetic causes of CMD has increased markedly. Previous classifications of the CMDs, which were based mainly upon the presence or absence of concomitant structural central nervous system abnormalities in addition to the muscular dystrophy, have largely been replaced by systems reflecting the underlying genetic abnormality and/or muscle pathology.

Infants with CMD usually present with neonatal hypotonia, often with arthrogryposis. MRI of the brain is often abnormal in the CMDs, showing changes suggestive of specific conditions. Muscle biopsy shows typical dystrophic changes while immunostaining may reflect deficiency of alpha-2 laminin (merosin) or alpha-dystroglycan (Godfrey et al. 2011).

Genetic testing may enable definitive diagnosis. In many individuals negative testing suggests additional genetic heterogeneity to that already identified. Most of the CMDs are recessively inherited, excepting the dominantly inherited forms of collagen 6A1, A2 and A3 muscular dystrophy (in ~50% of patients with Ullrich CMD) as well as LMNA MD.

Laminin alpha-two congenital muscular dystrophy (merosin-deficient CMD, merosin-deficient congenital muscular dystrophy (MDC1A)) was defined relatively early as a cause of CMD without structural brain or eye abnormalities – ‘classic’ CMD. Children with MDC1A have severe muscle weakness with onset in infancy, often with early joint contractures and scoliosis. Nocturnal hypoventilation is common. Most sit but few walk unsupported, while intelligence is normal (Pegoraro et al. 1998). This form of CMD is frequently associated with cerebral dysmyelination – seen on MRI – and with peripheral nerve demyelination. The associated gene, LAMA2, encodes the alpha-2 chain of laminin, also known as merosin, which is a part of the dystrophin-associated glycoprotein complex. Staining for this protein is absent or decreased on muscle biopsies of children with MDC1A (Mercuri et al. 2012).

Other forms of ‘classic’ CMD include the collagen VI-related CMDs (Ullrich and Bethlem CMD, UCMD and BM) which are characterized as associated with proximal joint contractures, striking distal hyperlaxity, sandpaper-like skin on the face and limbs, a characteristic facies and early-onset scoliosis. Children with Ullrich congenital muscular dystrophy are generally wheelchair-dependent by the end of the first decade; Bethlem myopathy has a similar but less severe phenotype. These conditions are on a phenotypic spectrum of ‘collagenopathies’ (Bushby et al. 2014). UCMD is caused in ~50% of individuals by recessive mutations in type VI collagen genes (COL6A1, COL6A2 and COL6A3), and Bethlem CMD generally dominantly inherited, although inheritance of both UCMD and BMD is variable (Giusti et al. 2005).

Recessive mutations in the selenoprotein N1 gene (SEPNI) cause rigid spine CMD associated with spinal rigidity and often with development of respiratory failure even while patients remain ambulant (Moghadaszadeh et al. 2001), while that associated with LMNA mutations often presents with severe weakness particularly affecting the neck extensors, and can be associated with life-threatening cardiac arrhythmias and cardiomyopathy as well as chronic respiratory insufficiency (Quijano-Roy et al. 2008).

The alpha-dystroglycanopathies are a genetically heterogeneous group of muscle disorders, all of which are associated with hypoglycosylated alpha-dystroglycan (ADG) on muscle biopsy. These conditions cause a range of phenotypes ranging from severe syndromal CMDs to later-onset limb-girdle muscular dystrophies (LGMDs) (Mercuri et al. 2009; Godfrey et al. 2011). The severe CMDs are often associated with developmental abnormalities of the eyes and brain, as seen in Walker-Warburg syndrome (WWS), muscle-eye-brain disease (MEB), and Fukuyama congenital muscular dystrophy (FCMD). Weakness in the alpha-dystroglycanopathies tends to be more pronounced in the upper than lower extremities.

Concomitant structural brain and ocular abnormalities, where present, often cause cognitive deficits, epilepsy and visual loss. Cardiac involvement is variably present and tends to be more severe in Fukuyama CMD, Walker-Warburg syndrome and muscle-eye-brain disease (Finsterer et al. 2010; Pane et al. 2012).

The serum creatine kinase is almost always markedly elevated in the dystroglycanopathies. Muscle biopsy shows classic dystrophic changes with absent or decreased staining for alpha-dystroglycan. A specific genetic diagnosis is often contingent on testing of multiple genes, which can most easily be achieved through next generation sequencing techniques.

The various genes involved in the dystroglycanopathies are listed in Table 26.2. Recent studies have shown that individual genes are commonly associated with different CMD phenotypes. Similarly, the defined clinical phenotypes are often associated with many different genes (Mercuri et al. 2009; Godfrey et al. 2011; Meilleur et al. 2014).

Fukuyama CMD (FCMD) is a severe disorder most often seen in Japan. Affected individuals have severe weakness, cognitive deficits, developmental delay, seizures and cardiomyopathy. Developmental brain anomalies in FCMD include occipital pachygyria and polymicrogyria, pontine hypoplasia and cerebellar abnormalities. Milder phenotypes are less commonly seen in children with FKTN mutations (Mercuri et al. 2006). In WWS muscle weakness is associated with severe brain and eye malformations, and hydrocephalus: this phenotype may be caused by mutations in the POMT1, POMT2, FKTN, FKRP, POMGNT1, LARGE, ISPD, GTDC2 and DAG1 genes (Mercuri and Muntoni 2012). Other mutations in POMT1 cause milder forms of congenital muscular dystrophy or an autosomal recessive form of LGMD. MEB, which has a milder phenotype than WWS, is also caused by mutations in a number of alpha-dystroglycanopathy genes (see Table 26.2).

Management of the CMDs follows guidelines for other neuromuscular disorders and is focussed on maintenance of strength and range of motion, with anticipatory monitoring for and treatment of disease-specific complications such as joint contractures, scoliosis, bulbar, respiratory and cardiac muscle involvement.
### Table 26.2  Congenital Muscular Dystrophies with identified gene loci

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMDs caused by protein defects</strong></td>
<td></td>
</tr>
<tr>
<td>Laminin-alpha 2 muscular dystrophy (MDC1A, merosin-deficient CMD, ( LAMA2 )-CMD)</td>
<td>Classic CMD</td>
</tr>
<tr>
<td>Collagen VI related dystrophies</td>
<td>Classic CMD with proximal contractures and distal hyperlaxity Ullrich muscular dystrophy (UCMD – 50% of cases AR) Bethlem myopathy (BM – generally AD)</td>
</tr>
<tr>
<td>SEPN1 related myopathy (RSMD1)</td>
<td>Classic CMD with rigid spine and early respiratory failure</td>
</tr>
<tr>
<td>LMNA related dystrophy (LMNA-CMD)</td>
<td>Classic CMD with dropped head Early-onset Emery–Dreifuss muscular dystrophy</td>
</tr>
<tr>
<td>Ryanodine-related CMD (RYR1-CMD)</td>
<td>Classic CMD, early scoliosis</td>
</tr>
<tr>
<td>Intergin ( \alpha )7-related CMD</td>
<td>CMD with axial and proximal muscle weakness</td>
</tr>
<tr>
<td>Intergin ( \alpha )9-related CMD</td>
<td>CMD with distal hyperlaxity and early scoliosis</td>
</tr>
<tr>
<td>Megoconial-type CMD</td>
<td>Mitochondrial CMD (CMDmt)</td>
</tr>
<tr>
<td><strong>Dystroglycanopathies</strong></td>
<td></td>
</tr>
<tr>
<td>( POMT1 )</td>
<td>WWS, MEB, CMD with/without intellectual disability, cerebellar anomalies, microcephaly</td>
</tr>
<tr>
<td>( POMT2 )</td>
<td>WWS, MEB, CMD with/without intellectual disability, cerebellar anomalies, microcephaly</td>
</tr>
<tr>
<td>( POMGNT1 )</td>
<td>WWS, MEB, CMD with/without intellectual disability</td>
</tr>
<tr>
<td>( FKTN )</td>
<td>Fukuyama CMD, WWS, CMD with/without intellectual disability</td>
</tr>
<tr>
<td>( FKRPP )</td>
<td>WWS, MEB, CMD with/without intellectual disability, microcephaly and cerebellar anomalies, LGMD</td>
</tr>
<tr>
<td>( LARGE )</td>
<td>WWS, MEB, CMD with/without intellectual disability, +/- cerebral dysmyelination</td>
</tr>
<tr>
<td>( ISPD )</td>
<td>WWS, MEB, LGMD</td>
</tr>
<tr>
<td>( GTDC2 )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( TMEM5 )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( B3GALNT2 )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( POMK )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( B3GNT1 )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( GMPPB )</td>
<td>WWS, MEB</td>
</tr>
<tr>
<td>( DAG1 )</td>
<td>CMD, LGMD with intellectual disability</td>
</tr>
<tr>
<td>( DPM2 )</td>
<td>CMD with intellectual disability, epilepsy</td>
</tr>
<tr>
<td>( DPM3 )</td>
<td>CMD with intellectual disability, epilepsy</td>
</tr>
<tr>
<td>( SGK196 )</td>
<td>MEB</td>
</tr>
<tr>
<td>( SGK196 )</td>
<td>MEB</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; LMNA, lamin A/C; CMD, congenital muscular dystrophy; WWS, Walker-Warburg syndrome; MEB, Muscle-Eye-Brain disease.
**PROGRESSIVE MUSCULAR DYSTROPHIES**

**DYSTROPHINOPATHIES (DUCHENNE AND BECKER MUSCULAR DYSTROPHIES)**

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy of childhood, affecting one in 5000 boys (Darras et al. 2015). Affected individuals present between 3 and 5 years of age with motor delay, gait abnormalities, frequent falls and difficulty arising from the ground. Less common presentations include language or global developmental delay, or an incidental finding of raised serum creatine kinase (creatine kinase) levels or hepatic transaminases. Boys with DMD lose the ability to walk by age 13 years.

Becker muscular dystrophy (BMD), a less common, milder phenocopy of DMD, is caused by mutations in the same gene – dystrophin – but is associated with independent ambulation beyond the age of 16 years. Other conditions caused by dystrophin mutations – ‘dystrophinopathies’ – include X-linked cardiomyopathy and isolated quadriceps myopathy (reviewed in Darras et al. 2015).

Weakness in DMD initially primarily affects the proximal lower limbs and trunk with later involvement of the upper limbs and distal muscles. Neck flexor weakness is usually present at presentation. Untreated boys with DMD cannot jump, with examination features including a waddling gait, prominent calves and a positive Gowers’ sign, the latter being a non-specific sign of proximal weakness after the age of 3 years. Most boys with DMD increase in strength and motor skills (albeit to a lesser extent than their peers) until about 6 years of age; after this stage progressive weakness is seen, to the point that most are wheelchair dependent by 13 years of age (Darras et al. 2015). Boys and men with BMD have more variable onset of weakness, some remaining ambulant throughout life.

Respiratory muscle involvement in DMD causes chronic restrictive lung disease which first manifests from around 12 years, causing a progressive decrease in lung capacity after that age (Khirani et al. 2014), which is exacerbated in those with severe scoliosis (Smith et al. 1989). Sleep-disordered breathing (SDB) in DMD may be caused by obstructive sleep apnoea in the first decade with invariable development of nocturnal hypoventilation in the second decade, followed by SDB with nocturnal hypercapnia then, finally, diurnal hypercapnia (Ragette et al. 2002).

Cardiac manifestations of the dystrophinopathies include dilated cardiomyopathy and arrhythmias. The first sign of cardiac involvement in DMD is a resting tachycardia which may be present in the first decade. Cardiomyopathy affects one-third of patients by age 14 years and all patients over 18 years of age but is generally asymptomatic because of generally low levels of physical activity in affected boys (Nigro et al. 1990). Symptomatic cardiomyopathy is much more common in BMD (Darras et al. 2005).

Overall, boys with DMD have a lower average IQ than their peers. Cognitive involvement in DMD and BMD affects verbal IQ more than performance IQ and is static throughout life (Liebowitz and Dubowitz 1981). DMD is also associated with a higher incidence of attention-deficit–hyperactivity disorder and autism spectrum disorders (Hendriksen et al. 2008).

Orthopaedic complications are virtually invariable in DMD. In the first decade of life a typical pattern of contractures commonly develops at the ankles, knees, iliotibial bands and hips, causing a characteristic lumbar lordosis and predisposition to toe-walking while affected boys remain ambulant. Scoliosis may develop in adolescence and can progress rapidly once boys are confined to a wheelchair, however it is now much less common than was the case before steroid treatment became the standard of care for DMD (Smith et al. 1989; Lebel et al. 2013). Fractures are common, especially in boys treated with steroids, and can precipitate permanent loss of independent ambulation (King et al. 2007; Darras et al. 2015).

Most female carriers of dystrophin mutations are asymptomatic. As many as 20% have mild to moderate muscle weakness and creatine kinase levels are raised in 50–60% (Hoogerwaard et al. 1999). Cardiac involvement may occur; up to 8% of carrier females develop a dilated cardiomyopathy in adulthood (Hoogerwaard et al. 1999a).

DMD is caused by mutations in dystrophin (DMD) gene on chromosome Xp21. The DMD gene is one of the largest genes known, containing 79 exons; the size of the gene makes it susceptible to mutations. Two-thirds of individuals affected by DMD inherit the gene maternally, one-third occurring as result of de novo mutations (Kunkel et al. 1986; Hoffman et al. 1987; Darras et al. 2015). Dystrophin localises to the skeletal muscle sarcolemmal membrane, complexing with the dystrophin-associated glycoprotein complex, and acting as a link between the cytoskeleton and the extracellular matrix (Rando 2001). Loss of dystrophin in DMD causes degeneration of muscle fibres and is likely to be as a result of cytoskeletal instability as well as abnormal calcium homeostasis (Deconinck and Dan 2007).

Mutations in DMD result in a truncated, unstable dystrophin protein product. The ‘reading frame rule’ explains the majority of the phenotypic differences between DMD and BMD; mutations disrupting the open reading frame cause a lack of any functional dystrophin, causing DMD, while those maintaining the open reading frame, with production of a lower molecular weight protein product retaining some protein function, cause BMD and the other dystrophinopathy phenotypes (Aartsma-Rus et al. 2006). Most (65–70%) patients with DMD have deletions; 10–15% have point mutations and about 5–7% have partial duplications of the dystrophin gene (Darras et al. 2015).

Serum creatine kinase levels are markedly raised in DMD, with levels 10–20 times the upper limit of normal seen from
birth. Serum alanine transaminase and aspartate transaminase levels are also raised; in boys with DMD these enzymes are muscle- (rather than liver-) derived; this can sometimes cause confusion (Bushby et al. 2010a). Deletions and duplications in the dystrophin gene can usually be detected by multiplex ligation-dependent probe amplification (MLPA) or high-resolution chromosomal microarray. Where these tests are negative, direct sequencing is required to identify point mutations in dystrophin; this method is relatively expensive and not available at all centres. Muscle biopsy is not required for diagnosis of DMD where genetic testing is conclusive but may be performed when genetic testing is negative. Typical muscle histology in DMD includes foci of muscle fibre necrosis and regeneration, with increased fibre size variability, mild inflammatory changes and replacement of muscle by fat and connective tissue. Immunostaining and/or Western blot analysis demonstrates a complete absence of dystrophin in DMD; milder changes are seen in BMD (Darras et al. 2015).

The multidisciplinary management of boys and young men with DMD revolves around symptomatic and rehabilitative management, monitoring for and treatment of the respiratory, cardiac, orthopaedic and nutritional issues associated with DMD and resulting corticosteroid treatment as well as genetic counselling. Advances in DMD management over the past two to three decades have improved both life expectancy and quality of life (Eagle et al. 2007; Passamano et al. 2012; Rall et al. 2012). International standards of care for the diagnosis and management of DMD were published in 2010, providing a benchmark for centres internationally and a basis for best practice care preparatory for clinical trials (Bushby et al. 2010a, b).

Maintenance of independent ambulation prevents development of contractures and scoliosis, while also helping to maintain independence (Darras et al. 2015). Regular physiotherapy and provision of orthotics prevent development or progression of contractures. Bone health assessments include monitoring of calcium, phosphate and 25-OH vitamin D levels, as well as bone densitometry in the steroid-treated and/or non-ambulant. Dietary supplementation of calcium and vitamin D should be considered in all boys, while boys with DMD should be monitored for development of scoliosis – both clinically and radiologically – once they become non-ambulant. Spinal fusion is considered in boys with a spinal curvature of greater than 20 degrees if they are still growing (Lebel et al. 2013). Patients with DMD have an increased risk of malignant hyperthermia-like reactions if exposed to inhalational anaesthetics and depolarising muscle relaxants; their parents and physicians must be aware of this risk (Hayes et al. 2008; Birkran 2009).

Monitoring of respiratory function in DMD should begin at 5–6 years of age, with consideration of annual overnight pulse oximetry or sleep studies once boys are non-ambulant. Acute respiratory infections require early management with antibiotics and chest physiotherapy (Birkran et al. 2009; Bushby et al. 2010a). Patients should be taught airway clearance techniques and offered support with nocturnal non-invasive ventilation (NIV) when they develop sleep-disordered breathing complicated by hypoventilation and/or hypercapnia. Benefits of NIV include fewer respiratory infections and hospital admissions, improved life expectancy and quality of life (Eagle et al. 2007; Young et al. 2007).

Cardiac surveillance in DMD includes regular electrocardiograms and echocardiograms, monitoring for arrhythmias and development of dilated cardiomyopathy (Nigro et al. 1990). Angiotensin converting enzyme inhibitors and/or beta blockers are increasingly used for treatment of left ventricular dysfunction (Angelini 2015). Boys on corticosteroids may require treatment for steroid-induced hypertension.

Supportive therapy for DMD includes appropriate attention to nutrition (Davidson and Truby 2009). Constipation, gastro-oesophageal reflux and dysphagia are common late in the disease course (Darras et al. 2015). Physical fitness is important for cognitive health and maintenance of cardiopulmonary function (Bushby et al. 2010a). Cognitive and mood issues may require input from a psychologist (Henriksen et al. 2008) while involvement of a palliative care team can help address social isolation, depression and pain towards the end of life (Bushby et al. 2010a).

Corticosteroids are the only pharmacological agent proven effective in DMD. Steroids improve muscle strength within 10 days of initiation of treatment; this improvement is maximal by 3 months (Glass et al. 2016). Ongoing corticosteroid therapy prolongs independent ambulation by up to 3 years, preserves cardiopulmonary function, reduces the risk of scoliosis and improves life expectancy in DMD (Balaban et al. 2005; Biggar et al. 2006; Manzur et al. 2008). The most commonly used corticosteroids are prednisolone and prednisone, at a dose of 0.75mg/kg/day. Deflazacort (0.9mg/kg/day), a synthetic corticosteroid, is used in some countries; the choice of corticosteroid used largely depends on availability, cost, formulation and side-effect profile (Glass et al. 2016).

The optimal age to begin treatment with corticosteroids is not clear. The current consensus is to start corticosteroid treatment at 4–6 years of age, prior to the onset of motor decline from DMD. Daily corticosteroid dosing is more effective than alternate daily dosing (Bushby et al. 2010a). Many centres continue corticosteroid treatment after loss of ambulation with the aims of preserving upper limb and cardiopulmonary function, as well as limiting progression of scoliosis (Pane et al. 2015). Long-term corticosteroid therapy has significant side-effects which should be monitored for and managed appropriately. The most common are excessive weight gain and behavioural problems; these can sometimes respond to a change in the steroid used (Glass et al. 2016). Growth suppression and delayed puberty are virtually universal, with boys treated with steroids at greater risk of vertebral and long bone fractures (Glass et al. 2016).

All affected families and possible carriers should be referred for genetic counselling. Prenatal diagnosis is available for carrier mothers who should also undergo cardiac monitoring in adulthood (Nolan et al. 2003; AAP 2005).

Recent clinical trials in DMD have focussed on gene therapies, stem cell therapies and dystrophin restoration approaches (Darras et al. 2015). Agents such as ataluren (Bushby et al. 2014) and antisense oligonucleotides (Mendell et al. 2013;
subtypes of DMD. Voit et al. 2014) remain under study but have shown promise in increasing muscle dystrophin expression in specific genetic subtypes of DMD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant myopathy characterised by progressive, frequently asymmetrical weakness involving the face, scapular muscles, proximal limb muscles and peronei (Tawil and Van der Maarel 2006). Typical initial symptoms are wasting of the shoulder girdle, winging of the scapulae, facial involvement with inability to purse the lips and close the eyes tightly, as well as a transverse smile. In the lower extremities there is generally a tendency to foot drop, with variable weakness of the hip girdle muscles. Respiratory function is usually normal while progression of weakness is insidious; many patients remain ambulant and life expectancy is usually unaffected. The respiratory muscles are usually only mildly affected.

The age at onset of FSHD is variable. Most patients first experience symptoms in the second decade but some remain asymptomatic throughout their lives. A small minority (4–5%) of patients have early onset (commonly called asymptomatic throughout their lives. A small minority experience symptoms in the second decade but some remain ambulant and life expectancy is usually unaffected. The respiratory muscles are usually only mildly affected.

The age at onset of FSHD is variable. Most patients first experience symptoms in the second decade but some remain asymptomatic throughout their lives. A small minority (4–5%) of patients have early onset (commonly called ‘infantile’ FSHD); this subgroup has more severe weakness generally associated with loss of independent ambulation by 10–12 years, severe restrictive lung disease and a predisposition to cardiac arrhythmias. Infantile FSHD is also associated with cognitive deficits, a retinal vasculopathy with telangiectasia and microaneurysms as well as high-frequency sensorineural hearing loss (Bailey et al. 1986; Brouwer et al. 1995; Padberg et al. 1995).

The serum creatine kinase is normal or only mildly elevated (3–5 times normal). Nerve conduction studies are normal; the EMG is mildly myopathic, showing low amplitude, short duration and polyphasic potentials. Where possible diagnosis should be made by genetic testing; muscle biopsy is not generally required but when undertaken demonstrates chronic myopathic changes, often with ‘inflammatory’ changes – significant mononuclear inflammatory infiltrates – resembling those seen in acquired inflammatory myopathies (Orrell 2011).

The genetics of FSHD are complex. Two (clinically indistinguishable) genetic subtypes are defined – FSHD1 and FSHD2 (Tawil et al. 2006; de Greef et al. 2010). Molecular testing is widely available and more than 95% of individuals with FSHD have a deletion within the tandemly arrayed D4Z4 repeat sequence on chromosome 4q35, detected by comparing the size of DNA fragments produced after digestion with the restriction enzyme EcoRI (Richards et al. 2012). This deletion results in loss of normal suppression of the double homeobox protein 4 gene (DUX4), normally expressed in germline tissue and epigenetically repressed in somatic cells (Tawil and Van Der Maarel 2006). The number of D4Z4 repeat units in the general population varies from 11 to 100 (EcoRI fragment $\leq 42$ kb). In patients with FSHD1 one D4Z4 allele is contracted (1–10 repeat units; EcoRI fragments $< 38$ kb) while the other D4Z4 allele is normal. Individuals with smaller EcoRI fragments (i.e. larger deletions) tend to have earlier onset disease and more rapid progression (Tawil et al. 2010). There are two equally common sequence variants of chromosome 4q, located adjacent to the D4Z4 region, and known as 4qA and 4qB (Lemmers et al. 2007; Lemmers et al. 2010). Only some haplotypes are pathogenic with respect to FSHD; contractions involving other 4qA and 4qB haplotypes are not pathogenic (Lemmers et al. 2002). A small minority of individuals with FSHD has DNA hypomethylation on both D4Z4 alleles, a condition called FSHD2, caused by mutations in the SMCHD1 gene (Lemmers et al. 2012). It is likely that both the D4Z4 deletion in FSHD1 and SMCHD1 mutations in FSHD2 affect DUX4 expression, leading to the development of FSHD by a toxic gain of function mechanism (Tawil and Van Der Maarel 2006; de Greef et al. 2010; Lemmers et al. 2012).

About 10–30% of individuals with FSHD have the disorder as the result of a de novo D4Z4 deletion; in the remainder there is a family history consistent with autosomal dominant inheritance (Bakker et al. 1996). The inheritance of FSHD2 is unclear but most cases appear to be sporadic (de Greef et al. 2010).

The distribution of weakness is an important clue to the diagnosis of FSHD, although similar findings may be seen in myotonic dystrophy, the congenital and mitochondrial myopathies, as well as some of the LGMDs (particularly LGMD 2A) (Tawil et al. 2010).

Management is primarily symptomatic, based on maintenance of strength, function and range of motion. Affected children need neuropsychological support for their cognitive deficits, and monitoring for ophthalmological, auditory, respiratory, cardiac and orthopaedic complications of their condition. Myalgia and joint pain are relatively common in FSHD and may respond to analgesics, physiotherapy as well as targeted exercise programmes (Tawil et al. 2010). Restrictive lung disease is more common in those with significant weakness while all persons with FSHD should be screened for retinal vascular disease at diagnosis; children require repeat studies until they are mature enough to report any visual loss (Statland et al. 2013). Children with FSHD should undergo regular audiological and ophthalmological reviews (Tawil et al. 2010).

EMERY-DREIFIUSS MUSCULAR DYSTROPHY

Emery-Dreifuss muscular dystrophy (EDMD) is an uncommon, genetically heterogeneous muscle disease with a characteristic clinical phenotype. Genes most frequently involved in this condition include EMDF, encoding emerin and FH1 (filamin-1), which cause X-linked EDMD. Autosomal dominant EDMD is caused by mutations in LMNA, the gene encoding laminas type A and C and by mutations in TMEM43, encoding LUMA. Mutations in two further genes, SYNE1 (nesprin 1) and SYNE2 (nesprin 2), may also cause rare variants of AD EDMD. Emerin, LUMA, lamin A and lamin C,
nesprin 1 and nesprin 2 are all proteins of the nuclear envelope (Puckelwanz and McNally 2011; Durmus et al. 2015).

Most children with EDMD present between 2–15 years although some develop symptoms later. The cardinal features of this condition include slowly progressive humero-peroneal muscle weakness and wasting, with early ankle and elbow contractures and back and neck stiffness (Durmus et al. 2015). Muscle weakness usually begins in the biceps and triceps, with subsequent development of peroneal muscle weakness and foot drop. Progression is slow but more than 10% of patients become non-ambulant in the third to fifth decades; their weakness may be exacerbated by spinal rigidity and joint contractures (Merlini et al. 1986). Disease severity can vary significantly within families.

Cardiac involvement in EDMD is often severe, particularly in those with LMNA mutations (Catrin et al. 2013). The ECG shows varying degrees of atrioventricular block with small T waves and atrial arrhythmias. Complete heart block often develops later and patients are at risk of atrial fibrillation, atrial flutter and atrial paralysis. Later, dilated cardiomyopathy and ventricular tachyarrhythmias can cause sudden death, even in those with minimal previous signs of cardiac disease (Sakata et al. 2005). The severity of cardiac involvement does not correlate with skeletal muscle weakness in EDMD (Durmus et al. 2015).

Creatine kinase levels are elevated, usually two to ten times normal. EMG shows typical myopathic changes. Muscle MRI can be useful in demonstrating selective muscle involvement. Muscle histology in all genetic subtypes shows a combination of myopathic and dystrophic changes, with type 1 fibre predominance and angular, atrophic fibres. Immunohistochemistry shows absence of staining for emerin in 95% of patients with X-linked EDMD (Yates and Wehner 1999). Molecular diagnosis of EDMD should be guided by use of defined algorithms given the genetic heterogeneity (Darras 2015).

Treatment is largely supportive. Contractures should be addressed with physiotherapy and orthopaedic interventions. All patients – even those with minimal muscle weakness – known carrier and at-risk family members should undergo regular cardiac surveillance with Holter monitoring and echocardiography. Development of a junctional bradycardia should prompt insertion of a pacemaker and implantable cardiac defibrillator. Patients with severe ventricular failure may be candidates for cardiac transplantation (Bonne et al. 2015). Respiratory involvement is significant in some individuals with EDMD; a minority develop nocturnal hypoventilation and require nocturnal ventilatory support.

**LIMB-GIRDLE MUSCULAR DYSTROPHIES**

The limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of disorders characterised by weakness and wasting of the pelvic and shoulder girdle muscles, with dystrophic muscle histology showing ongoing degeneration of muscle fibres, increased fibre size variability, fat and connective tissue. Even within specific genetic subtypes the clinical course of LGMDs varies markedly, from severe forms with rapid progression and onset in the first decade (similar to the clinical presentation of DMD) to milder forms with slower progression and later onset (for useful reviews see Bushby 2009; Pegoraro and Hoffman 2012). Most LGMDs cause predominantly proximal weakness, sparing the facial, extraocular and distal limb muscles.

The more common forms of LGMD are shown in Table 26.3. Most are recessively inherited (LGMD type 2) – a minority is inherited in an autosomal dominant fashion (type 1). The overall prevalence of LGMDs has been estimated at 2.27 per 100 000 persons (Norwood et al. 2009).

Most LGMDs involve proteins related to, or interacting with, dystrophin, such as the dystrophin-associated proteins (DAPs), α, β, δ- and γ-sarcoglycans. It is hypothesised that deficiency of any single component of the DAP complex disrupts binding of the extracellular matrix to the cytoskeleton, rendering the sarcolemmal membrane unstable and resulting in ongoing fibre necrosis (Zatz et al. 2003; Laval and Bushby 2004). Other LGMDs (LGMDs 2I, 2N, 2O and 2P) relate to aberrant glycosylation of α-dystroglycan, again resulting in loss of the link between the extracellular matrix and cytoskeleton, destabilising muscle fibres and predisposing to chronic dystrophic changes. A minority of LGMDs relate to other structural muscle proteins; dysferlin is involved in vesicle fusion in skeletal muscle (Bansal and Campbell 2004) while calpain is a calcium-sensitive intracellular protease; caveolin-3, a component of membrane lipid raft domains; lamin A/C and emerin, nuclear envelope proteins; telethonin and myotilin are sarcomeric proteins while TRIM32 is a putative ubiquitin ligase (Zatz et al. 2003). Abnormalities in these proteins may lead to disruption of cellular pathways, central to disease pathogenesis, rather than causing dystrophic changes in muscle by a direct effect on the structure and integrity of the sarcolemmal membrane.

**Clinical Correlates and an Approach to Diagnosis**

A detailed review of all of the different forms of LGMD is beyond the scope of this text but there are some clues that can aid the clinician in diagnosis (Table 26.3). The pattern of muscle involvement is important as can be the identification of additional findings such as joint contractures, cardiac and central nervous system involvement. A family history may suggest dominant or recessive inheritance and there is commonly significant inter- and intra-familial phenotypic variability in the LGMDs. Calf hypertrophy can occur in all groups but is rare in LGMD2B, in which calf atrophy may occur. Cardiac involvement (cardiomyopathy) is common in the sarcoglycanopathies and LGMDs type 2I, 2J and 1B. Early onset and more severe weakness (a Duchenne-like phenotype) can be seen in the sarcoglycanopathies and in LGMDs 2A and 2I while later childhood onset is suggestive...
of a calpainopathy, with adolescent/early adult onset suggesting a dysferlinopathy.

The differential diagnosis of the LGMDs includes Duchenne and Becker muscular dystrophies, myotonic dystrophy and FSHD. Affected females should be considered possible manifesting carriers of DMD. Other differential diagnoses such as juvenile acid maltase deficiency should be excluded by specific testing.

The creatine kinase is almost always raised in the LGMDs; the degree of creatine kinase elevation may be a clue to diagnosis. MRI may demonstrate specific muscle group involvement. Often the different forms of LGMD cannot be distinguished clinically, a specific diagnosis resting on protein studies on the muscle biopsy (immunohistochemistry and Western blot) to identify deficiency of a specific muscle protein, followed by mutation analysis to confirm the deficiency is due to a primary mutation in a specific gene (Table 26.3). Abnormalities seen on immunohistochemistry are not always specific and this semiquantitative test should be interpreted with caution; for example, dysferlin is abnormally localised

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### Table 26.3 The Limb-Girdle Muscular Dystrophies (LGMDs)

<table>
<thead>
<tr>
<th>LGMD type</th>
<th>Disease synonym</th>
<th>Relative frequency</th>
<th>Gene</th>
<th>Populations with founder mutations</th>
<th>Protein product</th>
<th>Distinguishing characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sarcoglycanopathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGMD2D</td>
<td>Alpha-sarcoglycanopathy</td>
<td>~70% of paediatric cases, 10% of adults</td>
<td>SGCA</td>
<td>Amish, North African, Brazilian</td>
<td>Alpha-sarcoglycan</td>
<td>Variable weakness, cramps, calf hypertrophy, cardiomyopathy, respiratory impairment</td>
</tr>
<tr>
<td>LGMD2E</td>
<td>Beta-sarcoglycanopathy</td>
<td></td>
<td>SGCB</td>
<td></td>
<td>Beta-sarcoglycan</td>
<td></td>
</tr>
<tr>
<td>LGMD2C</td>
<td>Gamma-sarcoglycanopathy</td>
<td></td>
<td>SGCG</td>
<td></td>
<td>Gamma-sarcoglycan</td>
<td></td>
</tr>
<tr>
<td>LGMD2F</td>
<td>Delta-sarcoglycanopathy</td>
<td></td>
<td>SGCD</td>
<td></td>
<td>Delta-sarcoglycan</td>
<td></td>
</tr>
<tr>
<td>LGMD2A</td>
<td>Calpainopathy</td>
<td>10%</td>
<td>CAPN3</td>
<td>Amish, Spanish, Turkish</td>
<td>Calpain-3</td>
<td>Proximal weakness, early contractures, scapular winging</td>
</tr>
<tr>
<td>LGMD2B</td>
<td>Dysferlinopathy</td>
<td>5%</td>
<td>DYSF</td>
<td>Jewish</td>
<td>Dysferlin</td>
<td>Distal weakness, calf atrophy</td>
</tr>
<tr>
<td>LGMD2I</td>
<td></td>
<td>5%</td>
<td>FKRP</td>
<td></td>
<td>FKRP</td>
<td>Calf hypertrophy, weakness upper&gt; lower extremities, cardiomyopathy, cerebral dysgenesis</td>
</tr>
<tr>
<td>LGMD2G</td>
<td>Telethoninopathy</td>
<td>Unknown</td>
<td>TCAP</td>
<td></td>
<td>Telethonin</td>
<td>Distal atrophy or calf hypertrophy, cardiomyopathy</td>
</tr>
<tr>
<td>LGMD2H</td>
<td></td>
<td>Rare</td>
<td>TRIM32</td>
<td>Manitoba Hutterites</td>
<td>TRIM32</td>
<td>Facial weakness</td>
</tr>
<tr>
<td>LGMD2J</td>
<td>Titinopathy</td>
<td>Unknown</td>
<td>TTN</td>
<td>Finnish</td>
<td>Titin</td>
<td>Cardiomyopathy and arrhythmias</td>
</tr>
<tr>
<td>LGMD2K</td>
<td></td>
<td>Unknown</td>
<td>POMT1</td>
<td>Turkish</td>
<td>POMT1</td>
<td>Intellectual disability, microcephaly</td>
</tr>
<tr>
<td>LGMD2L</td>
<td>Anoctaminopathy</td>
<td>Unknown</td>
<td>ANO5</td>
<td>European</td>
<td>Anoctamin-5</td>
<td>Asymmetrical weakness and wasting, knee hyperextension</td>
</tr>
<tr>
<td>LGMD2M</td>
<td></td>
<td>Unknown</td>
<td>FKTN</td>
<td></td>
<td>Fukutin</td>
<td>Steroid-responsive worsening after acute illnesses</td>
</tr>
<tr>
<td>LGMD2N</td>
<td></td>
<td>Unknown</td>
<td>POMT2</td>
<td></td>
<td>POMT2</td>
<td>Calf hypertrophy</td>
</tr>
<tr>
<td>LGMD2O</td>
<td></td>
<td></td>
<td>POMGnT1</td>
<td></td>
<td>POMGnT1</td>
<td>Calf hypertrophy</td>
</tr>
<tr>
<td>LGMD2P</td>
<td></td>
<td></td>
<td>POMGnT1</td>
<td></td>
<td>DAG1</td>
<td>Calf hypertrophy</td>
</tr>
<tr>
<td>LGMD2Q</td>
<td></td>
<td></td>
<td>PLEC</td>
<td>Turkish</td>
<td>Plectin</td>
<td></td>
</tr>
<tr>
<td>LGMD2T</td>
<td></td>
<td>Unknown</td>
<td>GMPPB</td>
<td></td>
<td>GMPPB</td>
<td></td>
</tr>
<tr>
<td>LGMD1A</td>
<td>Myotilinopathy</td>
<td></td>
<td>MYOT</td>
<td></td>
<td>Myotilin</td>
<td>Hyponasal speech, distal weakness</td>
</tr>
<tr>
<td>LGMD1B</td>
<td>Laminopathy</td>
<td></td>
<td>LMNA</td>
<td></td>
<td>Lamin A/C</td>
<td>Cardiac arrhythmias, cardiomyopathy</td>
</tr>
<tr>
<td>LGMD1C</td>
<td>Caveolinopathy</td>
<td></td>
<td>CAV3</td>
<td></td>
<td>Caveolin-3</td>
<td>Rippling muscles, cardiomyopathy</td>
</tr>
<tr>
<td>LGMD1D</td>
<td>Desminopathy</td>
<td></td>
<td>DES</td>
<td></td>
<td>Desmin</td>
<td>Cardiac conduction defects</td>
</tr>
<tr>
<td>LGMD1E</td>
<td></td>
<td></td>
<td>DNAJB6</td>
<td></td>
<td>DNAJB6</td>
<td></td>
</tr>
</tbody>
</table>
in up to 40% of LGMDs although complete deficiency as demonstrated by immunohistochemistry (IHC) is usually due to a primary dysferlin mutation (Bansal and Campbell 2004). Primary mutations in any one of the sarcoglycan genes can result in deficiency of all members of the sarcoglycan complex on IHC. Calpain deficiency demonstrated by Western blot is about 70% specific but can occur in other dystrophies; conversely, patients with mutations in the calpain gene have been identified in whom Western blotting for calpain is normal.

A specific diagnosis in the LGMDs is best made by molecular genetic testing, which is now most often done as part of a next-generation sequencing, panel or by whole exome sequencing which enable multiple genes to be tested in one iteration. These techniques may miss mutations involving large deletions or duplications.

### MYOTONIC DISEASES AND RELATED CONDITIONS

Myotonia is both a symptom and a sign. Clinically, myotonia manifests as delayed muscle relaxation which may be associated with a sensation of stiffness and/or discomfort. On electromyography myotonia is characterised by repetitive discharges producing classic ‘dive bomber’ (crescendo-decrescendo) discharges. Myotonia is caused by skeletal muscle fibre hyperexcitability, is purely of muscular origin and can be seen in a number of genetic diseases and syndromes including myotonic dystrophy and the ‘channelopathies’ or ion channel disorders.

### MYOTONIC DYSTROPHY (DYSTROPHIA MYOTONICA, DM1, STEINERT DISEASE)

Myotonic dystrophy is the most common myotonic myopathy, affecting around one in 7000 people. Milder cases are often undiagnosed. This multisystem disorder, transmitted as an autosomal dominant trait, affects skeletal and smooth muscle as well as the eye, heart, endocrine and central nervous systems. Findings in myotonic dystrophy span a continuum from mild to very severe and have been categorised into three (overlapping) phenotypes: mild, classic and congenital. Myotonic dystrophy type 1 is caused by a CTG trinucleotide expansion in the untranslated region of the dystrophia myotonica–protein kinase gene (DMPK) on chromosome 19q13.3. The length of this trinucleotide expansion may increase dramatically between generations (Harper 2001). Myotonic dystrophy type 2 (DM2, previously termed proximal myotonic myopathy) is a much less common disorder, which is not generally seen in childhood (Udd and Krahe 2012).

### CLASSIC MYOTONIC DYSTROPHY

Classic myotonic dystrophy has very variable clinical severity. The age at onset of classic myotonic dystrophy is typically in the twenties or thirties, although subtle early signs – facial weakness and the onset of myotonia – may be evident in childhood. Individuals with classic myotonic dystrophy type 1 (DM1) may have only cataracts, mild myotonia or diabetes mellitus (Harper 2001).

The distribution of muscular atrophy and weakness in myotonic dystrophy is characteristic. Atrophy of the facial muscles, especially the masseters and temporalis muscles, results in a long, thin face and hollowed temporal fossae, with the sternocleidomastoid and shoulder girdle muscles also involved. The brachioradialis muscles, hand intrinsics and muscles of the anterior compartment of the leg are also wasted, resulting in foot drop. In some patients weakness is mild, but those with significant symptoms in childhood tend to have progressive weakness in adult life, sometimes to the point of wheelchair confinement (Harper 2001; Echenne et al. 2008).

Muscle pain is often prominent in myotonic dystrophy. Myotonia, slowing of muscle relaxation after volitional contraction, is often best seen in the eyelids or after hand grip. Elicited myotonia is demonstrated by percussion of muscle (e.g. the thenar eminence, the thumb remaining opposed for several seconds after percussion).

Respiratory muscle compromise and aspiration may occur in individuals with advanced disease (Udd and Krahe 2012). Smooth muscle involvement in myotonic dystrophy may present with dysphagia, constipation, diarrhoea or incontinence. In adults frontal balding, hypogonadism and insulin resistance may occur (Hudson et al. 1987) with cardiac conduction defects the most important complication because of the risk of conduction block, cardiac arrhythmia and sudden cardiac death (Lund et al. 2014; Petri et al. 2014). Posterior cataracts develop after the first decade and may be the presenting feature of the disease. Intellectual impairment is common in patients with classic myotonic dystrophy; avoidant, obsessive-compulsive and passive-aggressive personality traits are also often seen (Serra et al. 2014). Hypersomnia and sleep apnoea are other well-recognised manifestations of the diseases (Udd and Krahe 2012). A reduced lifespan may be due to pneumonia and respiratory failure or cardiovascular complications such as arrhythmias (Groh et al. 2008).

### MILD MYOTONIC DYSTROPHY

Children with mild myotonic dystrophy may present with static cognitive issues prior to their later development of relatively mild, proximally-predominant muscle weakness.
(Ekstrom et al. 2009; Angeard et al. 2011). Myotonia may not be reported by patients when mild and has to be specifically looked for on examination.

**CONGENITAL MYOTONIC DYSTROPHY**

Congenital myotonic dystrophy is a severe myopathy of early childhood. The onset is prenatal with decreased fetal movement reflected in polydramnios, talipes equinovarus deformities and breech presentation. At delivery affected infants are hypotonic and weak, with facial diplegia and a tented upper lip (Fig. 26.1).

Children with congenital myopathies and congenital muscular dystrophies may look very similar to those with myotonic dystrophy although the overall appearance of the infant, especially distribution of facial weakness, is suggestive. Examination of the mother, for mild weakness and for myotonia, is the best clue to diagnosis.

Respiratory insufficiency due to diaphragmatic and intercostal muscle involvement occurs in about as many as 80% of individuals, necessitating ventilatory support and often leading to early death (Campbell et al. 2013). Most affected infants require gavage feeding (Campbell et al. 2013). Surviving infants gradually improve and usually eventually walk although they later develop a progressive myopathy, as in the classic form, and are at risk of cardiac arrhythmias and cardiomyopathy in the first decade of life (Igarashi et al. 1998; Bassez et al. 2004). Myotonia is never observed, even by EMG, before 3–4 years of age (often much later). Most children with congenital myotonic dystrophy have severe static cognitive deficits (Harper 2001; Echenne et al. 2008).

**Diagnosis and Treatment of Myotonic Dystrophies**

Serum creatine kinase is usually mildly to moderately elevated in DM1. In older children EMG is useful in identifying myotonic discharges which are most likely to be seen in distal muscles. Muscle biopsy is not generally required for diagnosis but when undertaken shows markedly increased internal nuclei and atrophic fibres with limited dystrophic changes. This can lead to the misdiagnosis of centronuclear myopathy.

DM1 is caused by expansion of a CTG trinucleotide repeat in the *DMPK* gene on chromosome 19q13.3 (Brook et al. 1992). The normal DMPK allele contains 5–34 CTG repeats. Adults with 35–49 repeats have a mutable normal (premutable) allele with their children at risk of inheriting a larger repeat size (Harper 2001). As is usual with disorders associated with DNA expansion, anticipation and a sex bias in genetic transmission are observed. The length of the repeat usually increases in successive generations, especially when maternally transmitted. There is a good correlation between the length of the expansion and the clinical severity and age at onset (Jaspert et al. 1995). Classic DM1 is associated with a repeat size of 100–1000 while congenital myotonic dystrophy is associated with repeat sizes >2000. Congenital DM1 is almost always inherited from the mother (Harper 2001).

Molecular genetic testing detects mutations in nearly 100% of affected individuals and enables pre- and postnatal diagnosis. The expanded CTG repeat leads to the abnormal processing of RNA transcripts that affect the alternative splicing and levels of expression of other genes, resulting in multisystem disease manifestations (e.g. chloride channel leading to myotonia, insulin receptor leading to diabetes) (Day and Ranum 2005).

Regular multidisciplinary disease surveillance is important for patients with myotonic dystrophy. Affected patients should undergo annual ECG and/or Holter monitoring to detect cardiac conduction defects as well as regular monitoring of pulmonary function and swallowing function. Many children require nutritional support and gavage feeding. Myotonia is rarely severe enough to require treatment while myalgia may require symptomatic treatment. Some children with DM1 experience excessive daytime sleepiness; this responds well to treatment with modafinil in adults but has not yet been formally studied in children (Annan et al. 2006).

Life expectancy is reduced in patients with congenital and childhood-onset myotonic dystrophy. Causes of death include pneumonia, sudden cardiac death and progressive respiratory failure (Mathieu et al. 1999; Groh et al. 2008) and as many as 25% of children with congenital myotonic dystrophy die before the age of 5 years, with only 50% surviving into their mid-thirties (Reardon et al. 1993). Very few achieve independent living as a result of the cognitive involvement.
A number of ion channel disorders affect skeletal muscle, variably producing myotonia and/or weakness. In diagnosing these conditions it is important to distinguish between myotonia and paramyotonia, with the former decreasing with repeated muscle contraction, know as the ‘warm-up’ phenomenon, while in paramyotonia or ‘paradoxical myotonia’ muscle relaxation becomes slower with repeated contractions (Cannon 2015).

This group of disorders can be considered as follows (Table 26.4):

1. Patients with clinical and neurophysiological evidence of myotonia who have dystrophic or non-dystrophic muscle disorders, with or without fixed muscle weakness.
2. Patients with electrical but not clinical evidence of myotonia, with this subset including a number of genetic and medication-induced myopathies.
3. Patients with suggestive symptoms but no clinical or electrical evidence of myotonia (Heatwole et al. 2013).

Myotonic muscle diseases causing weakness, myotonia and/or muscle hypertrophy are described briefly below.

### CHLORIDE CHANNEL DISORDERS

*Myotonia congenita* can be transmitted as either an autosomal dominant or autosomal recessive trait, or can occur sporadically as a result of de novo chloride channel gene mutations (Cannon 2015). Myotonia is present at the beginning of a movement after a period of rest, making movements difficult to initiate, but resolves after repeated movements. The severity of myotonia varies from mild symptoms causing no functional limitations to severe stiffness which significantly limits daily activities. Symptoms are often present from early childhood but may not be recognised until late adolescence or adulthood and are usually more significant in the legs and face than the arms. The recessive (Becker) form of this disease usually begins slightly later but is more severe than the dominant (Thomsen) form. Many patients have generalised muscle hypertrophy as a consequence of continuous muscle contraction. Stiffness is usually painless and increased by intense emotion or exposure to cold. Myotonic contraction can be elicited by percussion of muscles while serum creatine kinase may be normal or mildly elevated (three to four times upper limit of normal). Neither type of myotonia congenita is associated with the systemic features seen in myotonic dystrophy.

The clinical diagnosis is confirmed by EMG, which demonstrates repetitive discharges on insertion and with voluntary contraction: muscle biopsy is rarely necessary. Both the dominant and the recessive forms are caused by mutations in the voltage-gated chloride channel gene (*CLCN1*) on chromosome 7q (Koch et al. 1992). Sequencing of the *CLCN1* gene detects more than 95% of mutations in both forms of myotonia congenita.

Myotonia may be avoided by brief frequent periods of exercise and by avoidance of cold environments. In patients with problematic symptoms muscle stiffness may respond to
a variety of sodium-channel blocking agents including mexiletine, procainamide, tocainide and phenytoin (Heiman-Patterson et al. 2013). Depolarising muscle relaxants, adrenaline, beta-adrenergic agonists and propranolol may aggravate myotonia (Farbu et al. 2003). Malignant hyperthermia is reported in patients with myotonia congenita (Heiman-Patterson et al. 1988).

**SODIUM CHANNEL DISORDERS**

Several dominantly-inherited myotonic syndromes and periodic paralyses are caused by point mutations in the *SCN4A* gene on chromosome 17q23, encoding the voltage-gated skeletal muscle sodium channel (reviewed in Heatwole et al. 2013; Cannon 2015).

**Paramyotonia Congenita**

In this condition, myotonia is present from infancy and involves the eyelids, facial and hand muscles, as well as sometimes the pharyngeal muscles; all of these muscles are susceptible to the effects of cold (Cannon 2015). Characteristically, patients may be unable to reopen the eyes after several forceful closures in rapid succession. The myotonia may be increased by exercise (i.e. paradoxical myotonia). Many patients also experience episodic weakness and may develop muscular atrophy. Weakness is of two types: generalised episodes which can be brought on by cold, and localised weakness, provoked by exercise alone, which may occur in heat or cold.

Hyperkalaemic Periodic Paralysis is characterised by recurrent episodes of flaccid limb weakness, associated with an increase in the serum potassium during an attack of weakness, with normal muscle strength and serum potassium levels between episodes (Cannon 2015). Most patients are symptomatic before age 20 and the first presentation may be as early as infancy. Episodes of weakness are often triggered by moderate exercise and can last as short as a number of minutes or as long as a number of hours. Episodes may also be precipitated or worsened by potassium-rich food, rest after exercise, a cold environment, emotional stress or glucocorticoids. Mild myotonia is present between episodes in approximately 50% of individuals and is most readily observed in the eyelids, tenar muscles and finger extensors. The presence of myotonia suggests the diagnosis of hyperkalaemic periodic paralysis rather than other forms of familial periodic paralysis (Cannon 2015). Elevation of the plasma potassium during episodes may be difficult to document. Identification of myotonia on EMG supports the diagnosis but myotonia is detectable in only 50% of individuals affected – diagnostic yield is increased by testing at the onset of a symptomatic episode (Venance et al. 2006; Cannon 2015). The serum creatine kinase may be elevated to five to ten times normal concentration between episodes. Oral administration of potassium chloride after exercise may provoke an attack. Mutations in *SCN4A* account for only 60–70% of individuals, suggesting genetic heterogeneity.

The differential diagnosis includes other causes of hyperkalaemia such as adrenal insufficiency, medications (e.g. spironolactone, ACE inhibitors) and rhabdomyolysis. Andersen–Tawil syndrome is caused by mutations in the potassium channel gene *KCNJ2* (Venance et al. 2006) and characterised by episodic muscle weakness, ventricular arrhythmias and characteristic dysmorphic features (Tawil et al. 1994).

Episodes can be prevented or aborted by sustained mild exercise or carbohydrate loading at the onset of weakness. Other preventative measures include frequent carbohydrate-rich meals and avoidance of foods rich in potassium, fasting and exposure to cold. If episodes are frequent treatment with thiazide diuretics or acetazolamide may be considered (Heatwole et al. 2013).

**Other Potassium-Aggravated Myotonias**

These disorders are characterised by the development of stiffness following strenuous exercise or ingestion of potassium; all are associated with mutations in *SCN4A*. **Myotonia fluctuans**, the mildest form, resembles Thomsen disease with stiffness that is sometimes painful, precipitated by inactivity and resolving with continued exercise. Weakness is not a significant feature (Heatwole et al. 2013). In **acetazolamide-responsive** myotonia muscle pain may be induced by exercise (Heatwole et al. 2013). Myotonia permanens is a severe disorder associated with continuous myotonic activity on EMG which results in generalised muscle hypertrophy and may be confused with Schwartz–Jampel syndrome (Lehmann-Horn et al. 2004). **Normokalaemic periodic** paralysis resembles both hypo- and hyperkalaemic periodic paralysis but serum potassium levels during episodes are normal.

**CALCIUM CHANNEL DISORDERS**

Hypokalaemic periodic paralysis has two different forms, paralytic and myopathic, which may occur separately or together, with the pure version of the former more common. Most individuals present between age 5 and 16 years of age with infrequent episodes of weakness which are often precipitated by meals rich in carbohydrate or by exercise following rest and thus commonly occur in the early morning (Statland and Barohn 2013); exposure to cold may also be a trigger. The intensity and extent of weakness are very variable, with only the proximal limb muscles affected in some patients while others have diffuse paralysis; the facial muscles are rarely affected while the extra-ocular and respiratory muscles are usually spared. Some individuals have only one episode in a lifetime while crises occur more commonly on a repeated basis, often daily, weekly, or less frequently: most episodes last a few hours while some a day or more. In individuals affected severely the tendon reflexes are absent and muscles can be swollen. The episodes tend initially to increase in frequency then decrease after 25–30 years and may even disappear. The myopathic form of hypokalaemic periodic paralysis develops in approximately 25% of affected individuals, causing increasingly severe fixed muscle weakness that begins as exercise intolerance predominantly in the lower limbs. It occurs...
independently of the episodic paralysis and may be the sole manifestation of hypokalaemic periodic paralysis, however is not usually observed in children.

The diagnosis rests on the characteristics of paralysis and the family history. Potassium levels during episodes may be only slightly lowered and the creatine kinase is transiently elevated. The ECG reflects changes consistent with hypokalaemia: there is no myotonia, clinically or on EMG. Episodes may be provoked by administration of glucose and insulin, but a negative test does not exclude the diagnosis, with these tests not generally recommended in children.

Molecular genetic testing identifies mutations in the CACNA1S gene in about 70% of individuals (Cannon 2015), with about 12% of patients having mutations in the SCN4A gene (Jurkat-Rott et al. 2000). Mutations in these two genes are not found in around 20% of patients, raising the possibility of further genetic heterogeneity.

Hypokalaemic periodic paralysis is the most frequent cause of periodic paralysis but needs to be differentiated from causes of secondary hypokalaemia such as primary hyperaldosteronism, renal tubular defects and recurrent vomiting. In Asian patients hypokalaemic periodic paralysis is often associated with hyperthyroidism (Oh et al. 1990). Treatment of acute episodes is by oral potassium administration, 5–10 g per dose, which may be repeated. Prevention of episodes may be achieved by a low-carbohydrate and low-sodium diet and treatment with acetazolamide where necessary (Statland and Barohn 2013). Hypokalaemic periodic paralysis may be associated with an increased risk of malignant hyperthermia (Marchant et al. 2004).

CONDITIONS MIMICKING MYOTONIC MYOPATHIES

A number of unusual conditions present in childhood with muscle stiffness, hypertonia or pain without myotonia. These conditions are reviewed briefly below.

**Cramps** are involuntary painful contractions of a muscle or part of a muscle. When cramps occur in normal individuals they are usually confined to the distal lower extremities and characterised on EMG by the repetitive firing of normal motor unit potentials. Cramps are not associated with other symptoms or signs of neurological disease and are often precipitated by vigorous exercise or by excessive loss of fluids and electrolytes: stretching the involved muscle usually relieves the cramp. Night cramps are also physiological events although they occur much more frequently in children with neuropathies (Blyton et al. 2011).

**Pathological cramps** occur in association with a variety of metabolic disorders and secondary to disorders of the anterior horn cell, peripheral nerve or muscle itself (Taglia et al. 2015). Exercise-induced myalgia, with or without tenderness, exercise intolerance, weakness, cramps and myoglobinuria can occur in metabolic myopathies as well as in association with congenital myopathies, muscular dystrophies, inflammatory myopathies as well as toxic and endocrine myopathies.

**Myokymias** are rippling fascicular contractions that occur spontaneously in healthy children and adults, especially about the eyes but also in other muscles. They are a physiological phenomenon unless excessively diffuse and intense.

**RIPPLING MUSCLE DISEASE**

Rippling muscle disease (RMD) is characterised by ‘mounding’ produced by percussion of muscles and rolling muscle movements occurring after contraction followed by stretching, with muscle contractions being electrically silent: other clinical symptoms include muscle stiffness, cramps and pain on exercise. Although calf hypertrophy has been reported in RMD, muscle weakness and wasting is usually absent. Most individuals are affected as a result of autosomal dominant mutations in the gene encoding caveolin-3, which is also associated with LGMD type 1C (Milone et al. 2012).

**BRODY DISEASE**

Brody disease is a rare genetic myopathy that usually begins in childhood with progressive exercise-induced stiffness and myalgia (Karpati et al. 1986; Danon et al. 1988). The main clinical manifestation is difficulty in muscle relaxation which is different from myotonia in being electrically silent and increasing with continued exercise. Muscle biopsy shows only atrophy of type 2 fibres, with both autosomal recessive (Karpati et al. 1986) and autosomal dominant (Danon et al. 1988) kindreds described. The autosomal recessive form is now known to be due to mutations in the SERCA1 gene which encodes the sarcoplasmic reticulum calcium-activated ATPase of fast twitch muscles (Odermatt et al. 1996). Brody disease may be associated with malignant hyperthermia susceptibility (see below) (Sambuughin et al. 2014).

**PERIPHERAL HYPEREXCITABILITY AND ISAACS SYNDROME**

The terminology and nosology of the peripheral nerve hyperexcitability syndromes (PNH) are confusing. Hart et al. (2002) point out that many terms are used to describe the clinical manifestations of PNH such as neuromyotonia, Isaacs syndrome and cramp–fasciculation syndrome. All refer to a clinical phenomenon of abnormal, continuous muscle fibre activity of primary neural origin. Characteristic clinical accompaniments are muscle rippling or twitching, cramps, stiffness or delayed relaxation following voluntary muscle contraction (pseudo-myotonia). One electrical accompaniment is the neuromyotonic discharge, a burst of rapidly firing (150–300Hz) motor unit action potentials often starting or stopping abruptly with waning of the wave amplitude but not the waxing and waning pattern of myotonia. The discharges may occur spontaneously or be initiated by needle movement, voluntary effort or percussion of a nerve and can be abolished by nerve blocks. PNH is a feature of several rare diseases and syndromes for which pathogenetic mechanisms are progressively being defined; some are presumed auto-immune while others are clearly genetic (Kleopa 2011; Zimon et al. 2012).
Isaacs syndrome is a rare disorder of continuous motor unit activity, which in most individuals is an acquired channelopathy associated with antibodies against voltage-gated potassium channels (Hart et al. 2000). There is an association with other autoimmune disorders and neoplasms, notably myasthenia gravis and thymoma. The main clinical features are muscle stiffness, cramps and sweating; myokymia may also be seen, with the limbs and trunk most affected. This most affects adolescents but there are rare reports of onset in infancy with stiffness and respiratory difficulty (McGuire et al. 1984; Thomas et al. 1994; Gonzalez et al. 2008). The EMG shows continuous activity which appears to originate in the distal part of axons as it is not abolished by proximal nerve blocks, while there is neurophysiological evidence of a polynuropathy in up to a third of patients (Hart 2000). Treatment with anticonvulsants and immunotherapy may ameliorate symptoms (Hart 2000).

Stiff person syndrome

Stiff person syndrome is ordinarily a sporadic disease of adults with rare reports of childhood and adolescents being affected (Udani et al. 1997; Clardy et al. 2013; Jun et al. 2015). Progressive rigidity and painful muscle spasms develop primarily in the trunk and proximal limb muscles (Clardy et al. 2013), while there is also excessive sensitivity to external stimuli. Rigidity is always present except in sleep, with EMG of affected muscles showing continuous muscle fibre activity. There is an association with diabetes mellitus and other auto-immune disorders, with up to 80% of patients having autoantibodies to glutamic acid decarboxylase (GAD) which concentrates in GABAergic nerve terminals and in pancreatic cells. Benzodiazepines and baclofen provide symptomatic relief, longer-term amelioration being provided by immunotherapy with plasma exchange or intravenous immunoglobulin (Clardy et al. 2013; Jun et al. 2015).

Hyperkplexia

Hyperkplexia (see Chapter 9), sometimes referred to as the stiff baby syndrome, is characterised by severe stiffness and excessive startle which may be associated with prolonged apnoea in response to external stimuli (Mine et al. 2015). Most individuals affected by hyperkplexia present in the neonatal period. It is caused by mutations in the gene encoding the α1-subunit of the glycine receptor (GLRA1) on chromosome 5q31.2 and responds to treatment with clonazepam (Harvey et al. 2008).

Schwartz–Jampel syndrome

Schwartz–Jampel syndrome is an autosomal recessive condition featuring chondrodysplasia, short stature and continuous muscle contraction causing blepharophimosis, pursing of the mouth and puckering of the chin as well as stiffness of the limbs (Arya et al. 2013). The serum creatine kinase is normal or only mildly increased with EMG demonstrating abnormal muscle fibre activity and muscle histology usually normal. Treatment with sodium channel blockers may ameliorate symptoms (Arya et al. 2013). Schwartz-Jampel syndrome is caused by recessive mutations in the gene encoding perlecan (HSPG2), a heparan sulphate proteoglycan expressed in basement membranes and cartilage (Nicole et al. 2000).

Malignant Hyperthermia

Malignant hyperthermia is a pharmacogenomic disorder in which volatile anesthetic agents (e.g. halothane) or depolarising muscle relaxants such as succinylcholine trigger uncontrolled muscle contraction, potentially leading to life-threatening hyperthermia, muscle rigidity, acidosis, rhabdomyolysis and cardiac arrhythmias (Nelson and Litman 2014).

In nearly all individuals the first manifestations of malignant hyperthermia (masseter spasm, tachycardia and tachypnea) occur in the operating room but it may also feature in the early post-operative period. As the first exposure to these substances elicits an event in only 50% ofalignant hyperthermia-susceptible patients, a previous history of tolerance of halothane or succinylcholine does not ensure these agents can be used safely in future anaesthesia. Malignant hyperthermia is still the most frequent cause of death during anaesthesia.

The disorder is inherited as an autosomal dominant trait so a family history of suggestive incidents during anaesthesia is of extreme diagnostic importance. The syndrome may occur in two different settings: in patients with a genetic predisposition and those with specific muscular diseases. Malignant hyperthermia is most commonly associated with mutations of the skeletal muscle ryanodine receptor gene (RYR1) encoding the Ca²⁺ release channel of the sarcoplasmic reticulum (Robinson et al. 2006). Central core disease, King-Denborough syndrome and multiminicore myopathy, which can be caused by RYR1 mutations, are associated with an increased risk of malignant hyperthermia (McCarty et al. 2000; D’arcy et al. 2008; Brislin and Theroux 2013). On rare situations mutations have been identified in CACNA2D1, encoding dihydropyridine-sensitive L-type calcium channel alpha-2/delta subunits and in CACNA1S encoding the skeletal muscle calcium channel (Monnier et al. 1997): further loci have been mapped but the genes have not been identified while molecular genetic testing for RYR1 and CACNA1S is clinically available. Other conditions much less commonly linked to malignant hyperthermia include nemaline myopathy (Asai et al. 1992), Schwartz–Jampel syndrome (Seay and Ziter 1978), myoadenylate deaminase deficiency (Fishbein et al. 1985) and STAC3 myopathy (Dowling et al. 2014).

Because the underlying diagnosis is unknown in many patients undergoing muscle biopsy, malignant hyperthermia precautions should be taken in all patients prior to definitive diagnosis (Hayes et al. 2008; Racca et al. 2013; Rafique et al. 2013). Siblings and relatives of patients with malignant hyperthermia should be screened for high creatine kinase levels (Brandom and Muldoon 2013). Contracture testing, the standard diagnostic test for malignant hyperthermia since the mid-1970s, relies on the in vitro measurement of contractural...
response of biopsied muscle to graded concentrations of caffeine and the anaesthetic agent halothane. The sensitivity of the test approaches 100% with specificity between 80% and 97% (Allen et al. 1998). The in vitro contracture test requires a fresh muscle biopsy and is not well standardised in children.

The differential diagnosis of malignant hyperthermia includes sepsis, hyperthermia, pheochromocytoma crisis and thyrotoxicosis. Anaesthesia-induced rhabdomyolysis can occur in patients with dystrophinopathies but has a different pathophysiology from malignant hyperthermia (Hayes et al. 2008). Patients with myotonic syndromes can also develop muscle rigidity following succinylcholine administration.

Treatment for malignant hyperthermia includes termination of anaesthesia, body cooling, treatment of acidosis and intravenous injection of dantrolene at an initial dose of 1–2mg/kg, which may be repeated every 5–10 minutes up to a total dose of 10mg/kg (Racca et al. 2013).

**Neuroleptic Malignant Syndrome**

This syndrome shares several features with malignant hyperthermia. Affected children develop muscle rigidity, high fever and a raised serum creatine kinase after treatment with antipsychotic agents, including phenothiazines, clozapine and risperidone (Rasimas and Leibelt 2012). Sweating, tachypnoea, tachycardia, hypertension as well as altered consciousness develop over hours or days and can be complicated by development of renal failure secondary to rhabdomyolysis (Ty and Rothner 2004). Optimal treatment consists of early recognition, withdrawal of triggering medications and active supportive therapy. Bromocriptine and dantrolene reverse muscle hyperexcitability; levodopa and benzodiazepines are sometimes used (Halloran and Bernard 2004). Serotonin syndrome, secondary to treatment with selective serotonin reuptake inhibitors, can cause similar symptoms (Kant and Liebelt 2012): further molecular genetic testing may well clarify this possible association.

**Rhabdomyolysis and Myoglobinuria**

Myoglobinuria secondary to rhabdomyolysis is a rare phenomenon with a wide range of aetiologies but with potentially fatal physiological consequences irrespective of the acquired or inherited cause (Table 26.5, Fig. 26.5) (Chan et al. 2015).

Potential complications of rhabdomyolysis include acute renal failure, cardiac arrhythmias due to hyperkalaemia, bulbar muscle dysfunction, respiratory insufficiency and encephalopathy. The development of pigmenturia, sometimes with muscle pain and swelling, in a child with or without a previously recognised neuromuscular disorder therefore requires urgent medical attention. Apart from identifying myoglobin as the cause of the dark urine (reflected by a positive urine dipstick test for blood, but no red blood cells) a critically high creatine kinase level, often >100 times the upper limit of normal, is the cardinal clue to the nature of the problem. Although dipstick urine testing is sensitive, depending on timing, a negative test does not rule out myoglobinuria (Coco and Klasner 2004).

Exogenous causes such as direct or indirect injury, animal toxins (e.g. snake bite) and drugs are usually but not always obvious. The long list of causative drugs includes those of abuse and those associated with the neuroleptic malignant syndrome (Coco and Klasner 2004). Even after extensive investigation no cause may be found in many individuals but children have been classified into two broad groups on the basis of precipitating factors (Tein et al. 1990): exertion-triggered myoglobinuria in which a metabolic cause is often found, and ‘toxic’ myoglobinuria, precipitated by fever and infection. The latter group is generally younger, acutely tends to be more critically unwell and more often remains idopathic even after investigation. If there is no specific clinical clue to an aetiological diagnosis muscle biopsy after recovery from the acute episode of rhabdomyolysis may point in the direction of lipid storage, glycogen-related or mitochondrial myopathies (see Fig. 26.2).

**INFLAMMATORY MYOPATHIES**

The inflammatory myopathies are a heterogeneous group of acquired muscle disorders, all of which are individually rare in childhood.

**DERMATOMYOSITIS**

Dermatomyositis is a rare systemic microangiopathy mainly affecting capillaries of muscle, skin, connective tissue and gastrointestinal tract. The trigger for development of dermatomyositis is not known but immunopathogenesis hinges on activation of complement, with deposition of the membrane attack complex on the endomysium of small blood vessels and a localised microvasculitis.

Most individuals present between 5–15 years. Presentation is acute to subacute in one-third of individuals with fever, muscle pain and weakness. In the remaining patients the onset is more insidious with weakness, fatigue, anorexia and behavioural changes (Robinson and Reed 2011). Weakness in dermatomyositis dermatomyositis is generally proximally predominant and symmetrical: the bulbar muscles may be involved, causing hoarseness and swallowing difficulties (Robinson and Reed 2011; Kishi et al. 2013) while joint contractures may develop early and can be severe. Cutaneous manifestations of dermatomyositis include a photosensitive reddish lavender (‘heliotrope’, or violaceous) discoulouration of the skin of the upper eyelids, the periorbital and malar regions, with or without periorbital oedema. A similar rash, often scaly, may appear on the extensor surfaces of the knuckles (‘Gottron papules’), elbows, knees and malleoli of the ankles (Guseinova et al. 2011). A generalised
## Table 26.5 Causes of rhabdomyolysis in children

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<th>Acquired factors</th>
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<td>Infections</td>
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<td>Influenza, cytomegalovirus, Epstein-Barr virus, malaria, salmonella</td>
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<td>Inflammation</td>
<td>( \text{Inflammatory myopathies} )</td>
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<td>Muscle strain/activity</td>
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<td>Marathons, status dystonicus, convulsive seizures</td>
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<td>( \text{Medication-induced intense muscle activity} )</td>
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<td>Dystonic reactions, seizures</td>
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<td>( \text{Abrupt withdrawal of muscle tone-modifying treatment} )</td>
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<td>Baclofen withdrawal (oral, intrathecal), cessation of deep brain stimulation</td>
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<td>Myotoxins</td>
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<td>Neuroleptics, amphetamines, isotretinins, statins</td>
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<td>( \text{Malignant hyperthermia} )</td>
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<td>Use of depolarising agents/inhaled halogenated anaesthesia in those with predisposition (e.g. ryanodine receptor mutations; see inherited muscle disorders below)</td>
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<td>( \text{Neuroleptic malignant syndrome} )</td>
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<td>Other toxins</td>
<td>Licorice intoxication, carbon monoxide</td>
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<td>Metabolic</td>
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<td>Hypokalaemia, hypophosphataemia</td>
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<td>Environmental</td>
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<td>( \text{Near drowning and hypothermia} )</td>
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<td>Inherited muscle disorders predisposing to rhabdomyolysis</td>
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<td>Metabolic myopathy</td>
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<td>McArdle disease, myophosphorylase deficiency</td>
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<td>Tarui disease, phosphofructokinase deficiency</td>
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<td>Mitochondrial trifunctional protein combined enzyme deficiency, including LCHAD deficiency</td>
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<td>Muscle phosphatidic acid phosphatase deficiency (LPIN1)</td>
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<td>Mitochondrial disorders</td>
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<td>Muscular dystrophies</td>
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<td>Duchenne and Becker muscular dystrophies</td>
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<td>Ryanodine receptor 1 related myopathy</td>
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<td>Selenoprotein N related myopathy</td>
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Adapted from Chan et al. (2015). CPT, carnitine-palmitoyl transference; VLCAD, very long chain acylcoenzyme a dehydrogenase; MELAS, myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; FKRP, fukutin-related protein.
rash is rarely seen: the rash of dermatomyositis may be evanescent with diagnosis more difficult when cutaneous manifestations of dermatomyositis are not prominent or absent. Examination of the nailfold capillaries often shows dilated, tortuous vessels reflecting a generalised microangiopathy, especially in those with longstanding dermatomyositis (Smith et al. 2004).

Gastrointestinal symptoms are present in about 20% of patients, with bowel ulcerations being potentially fatal (Robinson and Reed 2011). Respiratory function is usually normal but occasional children experience respiratory distress from parenchymal lung disease (Robinson and Reed 2011).

Longstanding paediatric dermatomyositis may be associated with severe contractures, generalised wasting and chronic skin changes with thickened discoloured skin over the knuckles, generalised or focal lipodystrophic changes, osteoporosis and calcinosis of subcutaneous tissues.

In one series the median interval between onset of symptoms and diagnosis was 3 months with a range of 0.5–20.0 months (Pachman et al. 1998). Diagnosis is often delayed where cutaneous signs are absent, weakness is absent or not recognised, or presentation is with behavioural change.

Unlike adults, childhood dermatomyositis is not associated with malignancy (Robinson and Reed 2013).

The diagnosis of paediatric dermatomyositis is primarily clinical, based on the presence of acquired proximal weakness and the characteristic cutaneous findings (Smith et al. 2006). Tests used to confirm the diagnosis include nailfold capillaroscopy, muscle enzyme levels, magnetic resonance imaging (MRI) of the muscle, EMG and muscle biopsy.

Diagnostic criteria for dermatomyositis are based on the Bohan and Peter criteria (Bohan and Peter 1975), including a combination of clinical and laboratory findings as described above.

The serum muscle-derived enzymes (creatine kinase), lactate dehydrogenase (LDH), spartate aminotransferase (AST) and/or alanine aminotransferase (ALT), which are markers of muscle damage, are often but not always elevated in paediatric dermatomyositis. Screening for myositis-specific autoantibodies such as the anti-Jo1 antibody generally adds little to the diagnosis of juvenile dermatomyositis.

Nerve conduction studies are normal. EMG shows increased insertional activity with fibrillations and positive sharp waves and myopathic motor unit action potentials. These changes can be patchy and may be most obvious superficially within muscle bellies.

__Figure 26.2__ Dermatomyositis in childhood. Long standing disease is often complicated by (a,b) subcutaneous calcinosis while microvascular involvement can cause (c) infarction of small vessels in the skin and (d) Gottron papules over the joints.
Muscle imaging by ultrasound or MRI can be helpful, with muscle inflammation appearing as increased signal on ultrasound or T2-weighted fat-suppressed images (Tzaribachev et al. 2009).

Muscle biopsy is usually required to confirm the clinical diagnosis, even in apparently typical cases, prior to committing to potentially long-term immunosuppressive therapy. Capillary injury in dermatomyositis causes microinfarcts within muscle, causing muscle fibre injury, necrosis and regeneration, with a distinctive pattern of perifascicular atrophy (Robinson and Reed 2001). There may be perivascular mononuclear cell infiltrates within the muscle with endothelial necrosis. Immunocytochemical studies may demonstrate deposition of the membrane attack complex within muscle (Sakuta et al. 2005).

The differential diagnosis of paediatric dermatomyositis includes dystrophies such as Duchenne and Becker muscular dystrophy, as well as LGMDs. Some metabolic myopathies are associated with myalgia and exercise intolerance (see below). Other forms of myositis are rare in childhood; viral illnesses occasionally cause focal myositis which is generally self-limiting. Other rheumatological disorders are sometimes associated with myositis (see below).

The general aims of treatment are management of muscle inflammation, maximisation of function and prevention of contractures and calcinosis. Most data on prognosis in paediatric dermatomyositis are based on small observational studies; there are few prospective studies of outcome in paediatric dermatomyositis (Huber and Feldman 2005).

Most clinicians initiate treatment with high-dose corticosteroids (prednisolone, up to 1mg/kg/day), with or without concomitant treatment with intravenous immunoglobulin (IVIg). Methotrexate or cyclosporine are usually also used for longer-term control of dermatomyositis, increasing the effectiveness of treatment and limiting steroid-related side-effects (Stringer et al. 2010; Ruperto et al. 2016). Intravenous methylprednisolone may be initially substituted for prednisolone in some individuals with refractory weakness, severe gastrointestinal or respiratory involvement or rapidly progressive calcinosis (Rouster-Stevens et al. 2008), but should not be used for long-term treatment in the place of oral prednisolone (Klein-Gitelman et al. 2000). Severe ulcerating skin disease or severe systemic involvement (interstitial lung disease, gastrointestinal ulceration) may be treated emergently with intravenous cyclophosphamide or immunoglobulin. Other agents less commonly used in refractory juvenile dermatomyositis include rituximab and other biological agents.

Supportive therapy for paediatric dermatomyositis includes the use of sunscreen, topical agents for dermatomyositis-related rash (corticosteroid, tacrolimus or pimecrolimus creams), physiotherapy, occupational therapy as well as dietary supplementation of calcium (1000mg/day) and vitamin D (1000 units/day) to prevent osteoporosis. Calcinosis of soft tissues is best prevented by immunosuppressive therapy of dermatomyositis; no consistently effective treatments have been identified.

Typical disease courses in paediatric dermatomyositis include a monophasic illness with sustained response to therapy, a relapsing-remitting course or (most commonly) a chronic illness with increasing deficits over time. Response to treatment is determined by evaluating muscle strength, changes in rashes, and muscle enzyme testing. Serial muscle strength testing is best done using standardised scales such as the MMT8 or Childhood Myositis Assessment Scales (Lovell et al. 1999; Rider et al. 2010). Muscle MRI also shows some promise as a means of following disease progression in dermatomyositis (Malattia et al. 2014).

The prognosis of paediatric dermatomyositis has improved markedly in the last 3–4 decades. Prognosis is poorer in those with greater severity at presentation, ulcerating skin lesions and gastrointestinal involvement (Huber and Feldman 2005).

OTHER MYOSITIDES OF CHILDHOOD

Macrophagic myofasciitis is a rare inflammatory myositis presenting in infants and young children with delayed motor milestones, hypotonia and high creatine kinase. It is thought to be connected to aluminium hydroxide-containing vaccines which have usually been administered in the 1–2 months before the onset of symptoms. Muscle biopsy shows large collections of perimysial macrophages (Gruis et al. 2006; Lach et al. 2008).

Polymyositis, another inflammatory myopathy, albeit without skin rash and with a different immunological basis to dermatomyositis, is very rarely, if ever, seen in children. In those children experiencing progressive muscle weakness (especially distal weakness) without rash, in whom apparently inflammatory changes are seen on biopsy, diagnostic efforts should be directed towards facioscapulohumeral muscular dystrophy and other genetic myopathies in which such pathological findings may be seen (D’Arcy et al. 2009; Tarnopolsky et al. 2016).

INFLAMMATORY MYOPATHIES ASSOCIATED WITH SYSTEMIC DISEASE

Some systemic connective disorders can be associated with a myopathy in childhood.

Rheumatoid arthritis, scleroderma-myositis, systemic lupus erythematosus-myositis, mixed connective disease-myositis, Churg-Strauss syndrome and Sjögren syndrome-myositis can all be associated with proximal weakness which can be severe and may be associated with calcinosis, interstitial lung disease, arthritis and sclerodactyly (Mason and de Vivo 2015). Treatment is of the underlying condition but morbidity can be severe.

Other autoimmune disorders uncommonly associated with myositis in childhood include Kawasaki disease, Behcet syndrome and Wegener granulomatosis.
EOSINOPHILIC MYOPATHIES

A number of eosinophilic myopathies have been reported in childhood. Idiopathic eosinophilic myositis can be focal or generalised, presenting with myalgia, muscle swelling and weakness, sometimes in association with systemic upset. In eosinophilic myositis muscle weakness can be associated with pericarditis, myocarditis, cardiac arrhythmias and skin involvement (angiœdema and subcutaneous induration). There may be peripheral blood eosinophilia in addition to elevated creatine kinase levels and localised myopathic EMG changes (Pickering and Walport 1998).

Eosinophilic myopathies are also associated with parasitic infections (Taenia solium and Trichinella spiralis), ingestion of toxic oils (Alonso-Ruiz et al. 1993) and dietary supplementation with tryptophan (Hertzman et al. 1990).

FOCAL MYOSITIS

Focal myositis is a rare syndrome in which children develop localised swelling and pain in a single muscle group, sometimes after trauma, often raising the question as to a neoplastic or infectious process (Isaacson et al. 1991). Imaging studies define the extent of the lesion (Galloway et al. 2001) but muscle biopsy is generally required to confirm the diagnosis, showing increased fibre size variation with atrophic fibres and foci of dense fibrosis (Forcucci et al. 2016). Lesions may resolve spontaneously or may require surgical excision (Forcucci et al. 2016).

INFECTION MYOSITIS

VIRAL MYOSITIS

Epidemic pleurodynia (Bornholm disease) due to Coxsackie virus B infection is a well-recognised disease involving the intercostal muscles (Huang et al. 2010). Myalgia is common in some other viral diseases, especially influenza. A more diffuse picture of acute diffuse polymyositis is uncommon and individuals affected severely by myoglobinuria are rare (Moon et al. 2013). Other viruses (adenoviruses, parainfluenza viruses) rarely produce myositis.

Benign acute childhood myositis (Mackay et al. 1999) is an easily recognisable syndrome of mid-childhood affecting boys more than girls. A concurrent or preceding (1–4 days) upper respiratory infection is typically followed by the sudden onset of calf pain and tenderness, with refusal to walk or difficulty walking. The gait pattern is usually either toe-walking with resistance to passive ankle dorsiflexion or walking in extreme recurvatum at the knees, possibly to minimise stretch of the gastrocnemius-soleus complex. More proximal lower limb and upper limb muscles may also be involved but it is the calf muscle predilection that gives the syndrome a recognisable pattern. Weakness and difficulty eliciting deep tendon reflexes are commonly described but generally relate to difficulty in examining a child with severe discomfort (Mackay et al. 2009; Mall et al. 2011): an erroneous diagnosis of Guillain–Barré syndrome is often made. The child may be febrile and there may be elevation of the acute phase reactants while the serum creatine kinase may be only mildly elevated or increased to levels as high as 60 times the upper limit of normal. The creatine kinase level returns to normal in the convalescent period with most children recovering fully within days and only a minority experiencing repeated episodes which may raise the question of an underlying myopathy, a disorder occurring sporadically or in epidemics. Associated viruses include influenza A and B as well as less commonly parainfluenza, adenovirus and coxsackie infection. Muscle biopsy may show inflammatory and other non-specific changes but should not be required for diagnosis. The importance of recognising this syndrome is in avoiding unnecessary investigation and signalling a good prognosis to the family.

BACTERIAL MYOSITIS (PYOMYOSITIS)

Purulent myositis is common in tropical countries and is becoming more common in temperate climates, for reasons which are unclear (Unnikrishnan et al. 2010; Moriarty et al. 2015). Most individuals are affected as a result of infection with Staphylococcus aureus, with abscess formation occurring following a phase of muscle induration. Early diagnosis and differentiation from other conditions such as septic arthritis and rhabdomyosarcoma has become easier with the use of modern imaging technologies, especially MRI. Surgical drainage may be necessary, in addition to antibiotic treatment, with the course usually favourable (Pannara et al. 2006; Moriarty et al. 2015). Non-suppurative myositis is also observed in individuals affected by Borrelia burgdorferi infection (Holmgren and Matteson 2006).

PARASITIC MYOSITIS

Trichinosis is the most common cause of parasitic myositis (Pickering and Walport 1998). Muscle involvement in cysticercosis can present with myalgia, nodular lesions or muscle pseudohypertrophy. Ultrasound or X-rays may show nodules or calcified cysts while muscle biopsy reveals cysterci within the muscle (Venkataraman and Vijayan 1983). Toxoplasmosis is an unusual cause of inflammatory myopathy (Paspalaki et al. 2001).
Metabolic myopathies are conditions in which disordered energy production by muscle results in weakness and often myalgia. Disorders of glycogen or lipid metabolism or mitochondrial function may involve muscle, either as an isolated phenomenon or as part of a multisystem syndrome. The associated myopathy may be permanent with progressive weakness or may be intermittently symptomatic with episodes of myalgia, rhabdomyolysis and myoglobinuria often being triggered by exercise or other factors. Although the clinical features may be easily identified the underlying metabolic defect may be difficult to establish because of the complexity of the laboratory analyses required (see also Chapter 9). Despite detailed knowledge of the biochemical and genetic basis of some of these disorders effective treatments are still quite limited.

ACID MALTASE DEFICIENCY

Acid maltase (acid α-glucosidase); (GSD-II) is a lysosomal enzyme present in all tissues which catalyses the hydrolysis of α-1,4 and α-1,6 linkages, breaking glycogen down into glucose. Deficiency of this enzyme results in glycogen accumulation in the tongue, heart and skeletal muscles. The clinical syndromes associated with this condition included a severe infantile form (Pompe disease) and a milder form of acid maltase deficiency presenting in childhood or adulthood. Both conditions result from autosomal recessive mutations in the same gene, GAA (chromosome 17q25.2–q25.3) (Kishnani and Howell 2004).

The infantile form of acid maltase deficiency, known as Pompe disease or type Iα glycogenesis, presents at around 1–2 months of age with profound hypotonia, failure to thrive, weakness, macroglossia, progressive cardiomyopathy and cardiac failure which may be the presenting feature. Areflexia is present in one-third of patients at presentation as a result of anterior horn cell involvement. Most infants never achieve the ability to roll. The serum creatine kinase level may be normal but is usually elevated while the ECG shows a short P-R interval, giant QRS complexes and left or biventricular hypertrophy, often with inverted T waves and/or ST depression. Most children die from cardiorespiratory failure before the age of 12 months (Kishnani and Howell 2004).

In the later-onset form patients present with slowly progressive trunk and proximal limb weakness. Mild hypertrophy of the calves may cause confusion with one of the muscular dystrophies. The respiratory muscles are involved relatively early, often causing respiratory failure by the second or third decade, but the heart is spared in this form of acid maltase deficiency. Many affected individuals ultimately become wheelchair-dependent and require ventilatory support (Laforet et al. 2013) while late complications of this condition in adulthood may include large vessel aneurysms and smooth muscle involvement (Angelini and Semplicini 2012; Laforet et al. 2013).

The creatine kinase is elevated in both forms of acid maltase deficiency. EMG generally shows a myopathic interference pattern, often with complex repetitive discharges and myotonic discharges in the paraspinal and proximal limb muscles. Muscle MRI can be helpful in identifying typical patterns of muscle involvement (Carlier et al. 2011). Biopsy shows a vacuolar myopathy and decreased α-glucosidase levels (<10% normal activity) are seen on assay of muscle, leukocytes or fibroblasts. A large number of mutations have been found in the α-glucosidase gene: prenatal diagnosis is possible on trophoblasts or amniotic cells.

Enzyme replacement therapy with recombinant human α-glucosidase has been shown to result in improved walking distances and stabilisation of respiratory function in late-onset patients (de Vries et al. 2012). Infants with Pompe disease have prolonged survival with ERT but generally remain very weak and ventilator-dependent and there are concerns about their long-term cognitive outcome (Elbink et al. 2016).

DEBRANCHER DEFICIENCY AND BRANCHER DEFICIENCY

Debrancher deficiency (GSD-III and Brancher deficiency (GSD-IV) are usually characterised by predominant liver disease, presenting as hepatomegaly, growth failure and fasting hypoglycaemia. Affected infants may be hypotonic with motor
delay or muscle weakness, that is, may not be seen until later in life without a preceding history of liver disease. Affected children have generalised weakness with exercise intolerance and cramps while adults tend to have predominantly distal weakness. Muscle biopsy shows a vacuolar myopathy while sequencing of the \textit{AGL} gene on chromosome 1p12 is diagnostic. Dietary management may include frequent meals, administration of uncooked cornstarch and continuous gastric drip feeding (Sentner et al. 2016).

Glycogen storage disease type IV (GSD-IV), is an autosomal recessive disorder due to mutations in the glycogen branching enzyme gene (\textit{GBE1}, chromosome 3p12). An amylopectin-like polysaccharide known as polyglucosan is accumulated. The perinatal form presents as fetal akinesia deformation sequence (FADS) with multiple joint contractures, hydrops fetalis and perinatal death (Escobar et al. 2012). The congenital form includes hypotonia, hyporeflexia, cardiomyopathy, ventilator dependence and cardiorespiratory death in early infancy (Bruno et al. 2004; Giuffrè et al. 2004). Later-onset forms present with hepatic disease and progressive cirrhosis with \textit{variable myopathy or cardiomyopathy} (Bruno et al. 2004).

\textbf{McARDLE DISEASE}

Muscle phosphorylase initiates glycogen breakdown by removing 1,4-glucosyl residues from the outer branches of the glycogen molecule, releasing glucose-1-phosphate. The deficiency causes Mc Ardle disease (myophosphorylase deficiency: GSD-V), the prototype of the glycogenoses manifesting with intermittent symptoms. Mc Ardle disease, which shows autosomal recessive inheritance, is caused by many different mutations of the \textit{PYGM} gene on chromosome 11q13. The incidence of the disease is one per 50 000 births (Tsujino et al. 1993).

The onset, frequently not recognised as such for many years, is usually in the first two decades. The cardinal clinical features are exercise intolerance with fatigue, muscle pain and cramps developing soon after initiating exercise. Exercise precipitating symptoms is generally either brief and intense or sustained and less intense. Most patients experience a characteristic ‘second wind’ phenomenon: if they rest briefly after the onset of symptoms; they can then resume without redeveloping myalgia or fatigue. This phenomenon largely results from the switch from use of glucose to free fatty acids as a substrate of muscle metabolism. Episodic weakness after exercise can be associated with rhabdomyolysis leading to myoglobinuria and, if severe, acute renal failure. In children, however, easy fatigability can be the only symptom: most children reduce their overall level of physical activity as a result of pain. Permanent weakness may be observed after many years, particularly if there are repeated episodes of rhabdomyolysis.

Rare patients have variant phenotypes such as a congenital myopathy presenting with delayed milestones (Cornelio et al. 1983) or slowly progressive proximal weakness with onset in childhood but without myalgia or myoglobinuria (Abarbanel et al. 1987). A fatal infantile type has been described (Milstein et al. 1989; El-Schahawi et al. 1997) while occasional asymptomatic patients are identified as a result of elevated creatine kinase levels (Oldfors and DiMauro 2013).

The creatine kinase is moderately increased in most patients at rest but may rise dramatically after exercise, particularly in the context of myoglobinuria. The EMG may be normal or myopathic while the non-ischaemic forearm exercise test can be used as a screening test, showing failure of the usual rise in the serum lactate level with an increase in ammonia (Chan et al. 2015). Muscle biopsy shows a moderate increase in subsarcolemmal glycogen and the absence of phosphorylase can be demonstrated histochemically (Darras and Friedman 2000a). Gene testing is generally available.

There are no specific treatments for Mc Ardle disease. Patients with residual enzyme activity may benefit from dietary vitamin B6 supplementation; pyridoxal phosphate binds to myophosphorylase (Oldfors and diMauro 2013). Low-dose creatine (60mg/kg/day for adults) and oral sucrose taken 30 minutes before exercise may alleviate some symptoms. A carbohydrate-rich diet seems more effective than a high-protein diet while regular moderate exercise improves metabolic capacity and exercise tolerance (Quinlivan et al. 2014).

\textbf{PHOSPHFRUCTOKINASE DEFICIENCY, OR TARUI DISEASE)\n
Phosphofructokinase deficiency (GSD-VII) is due to mutations in the M (muscle) subunit of the phosphofructokinase enzyme, for which the gene \textit{PFKM} is located on chromosome 12q13.3: in muscle only M subunits are present. Both M and L subunits are found in erythrocytes; hence, in addition to muscle symptoms, M subunit deficiencies may also present with bouts of haemolytic anaemia and hyperuricaemia. Impaired glycolysis leads to cramps on exercise and myoglobinuria (Di Mauro 2007) similar to Mc Ardle disease but these patients are unable to achieve a spontaneous second wind under conditions that consistently produce one in patients with Mc Ardle disease. In addition, their symptoms are often worsened rather than ameliorated by high carbohydrate intake (Haller and Vissing 2004).

A severe neonatal form is marked by hypotonia, weakness, respiratory insufficiency and joint deformities. Cerebral involvement is present and death supervenes during the first year (Servidei et al. 1986; Amit et al. 1992). There is no specific therapy for PFK deficiency (Musumeci et al. 2012).

\textbf{PHOSPHORYLASE B KINASE DEFICIENCY}

Phosphorylase B kinase (PKB) (GSD-VIII) regulates glycogen breakdown by activating glycogen phosphorylase in response to humeral (neural or hormonal) stimuli: this enzyme has four subunits. Muscle involvement is described with mutations of the beta subunit of the \textit{PHKB} gene on chromosome 16q12–q13. PKB deficiency is uncommon; onset of symptoms may
be in infancy or early childhood with weakness and delayed motor milestones or later in childhood or adolescence with exercise intolerance, cramps and episodic myoglobinuria (DiMauro 2007). There may be liver involvement while severe myopathy presenting in the neonatal period has been described (Sahin et al. 1998; Bühler et al. 2000). Creatine kinase levels, non-ischaemic exercise testing and muscle histology are sometimes normal, which is likely to cause diagnostic difficulty (Wilkinson et al. 1994).

**DISORDERS OF LIPID UTILISATION AND METABOLISM**

Fatty acids are very important fuels for skeletal muscle, particularly during sustained exercise and under fasting conditions (see also Chapter 9). Defects in fatty acid oxidation cause progressive myopathies, recurrent rhabdomyolysis, neuropathies and cardiomyopathy in addition to hypoglycaemic hypoketonotic episodes and seizures. At least 16 genetic disorders of fatty acid oxidation are recognised, with a combined incidence of about one in 9300: all are inherited in an autosomal recessive fashion (Tein 2013). Carnitine is an essential cofactor in the transfer of long-chain fatty acids into the mitochondrion where fatty acids of long, medium and short chain are metabolised by beta-oxidation.

**CARNITINE DEFICIENCY**

Carnitine deficiency is often secondary to other metabolic disorders (Chapter 9) but can occur as a primary defect.

**OTHER GLYCOCENOSES**

Myopathy presenting with intolerance to exercise and associated myoglobinuria has been reported in phosphoglycerate mutase deficiency (GSD-X) (PGAM-M gene, chromosome 7p12–p13) (Vita et al. 1994; Hadjigeorgiou et al. 1999), lactate dehydrogenase deficiency (GSD-XI) (LDHA gene, chromosome 11p15.4) (Oldfors and DiMauro 2013) and phosphoglycerate kinase deficiency (GSD-IX) (PGK1 gene, chromosome Xq13) (Sugie et al. 1989; Aasly et al. 2000).

**MYOADENYLATE DEAMINASE DEFICIENCY**

Myoadenylate deaminase deficiency (MADA) (AMPD1 gene, chromosome 1p13–p21) is an autosomal recessive trait found in 1–2% of the population. Most carriers are asymptomatic but some experience myalgia, exercise intolerance and weakness: this variability is not yet well explained (Sabina 2000). The diagnosis is suggested by non-ischaemic forearm exercise testing showing normal lactate production with failure of the blood ammonia level to rise (Chan et al. 2015), confirmed on muscle biopsy.

**-primary Carnitine Deficiency**

Primary carnitine deficiency is an autosomal recessive disorder with progressive proximal limb weakness, often associated with cardiomyopathy and fasting hypoglycaemia. Muscle biopsy shows lipid storage and reduced carnitine content. Dietary treatment with L-carnitine is generally effective (Tein 2013).

**DEFICITS IN CARNITINE-PALMITOYL TRANSFERASE**

The carnitine-palmityl transferase (CPT) system includes two enzymes, defects of which limit entry of long-chain fatty acids into mitochondria. CPT I deficiency is rare but has been identified in a few patients presenting with episodes of severe hypoglycaemia without ketosis, triggered by fasting or intercurrent illnesses.

CPT II deficiency, a much more common disorder, may present as a lethal neonatal form limited to muscle (Land et al. 1995) or associated with CNS malformations (Isackson et al. 2008) in infancy with hepatic and cardiac involvement as well as non-ketotic hypoglycaemia, or as a clinically quite different later onset form (Sigauke et al. 2003). The late-onset (classic) form of CPT II deficiency, which is the most common, is dominated by episodic weakness, myalgia and myoglobinuria and very high creatine kinase levels. Muscle strength and the serum creatine kinase are usually normal between episodes and there is no ‘second wind’ phenomenon. Onset is usually in late childhood or early adulthood but presentation in the first few years of life has been described (Hurvitz et al. 2000; Gempel et al. 2001). Prolonged exercise, fasting, fever or infections may trigger symptoms while the respiratory muscles may be involved: death during an attack in childhood has also been reported (Kelly et al. 1989). There is a marked reduction or complete absence of CPTII enzyme activity in muscle as well as in leukocytes, platelets and cultured fibroblasts.

Many mutations have been described in the CPT II gene on chromosome 1p32 (Sigauke et al. 2003). A similar clinical picture to that of CPT II deficiency may be seen with mitochondrial trifunctional protein (long-chain 3-hydroxyacyl-CoA dehydrogenase) deficiency (Schaef er et al. 1996; Miyajima et al. 1997). Treatment consists mainly of avoidance of fasting or other triggering factors and ingestion of a high-carbohydrate, low-fat diet. Treatment with bezafibrate shows promise in reducing biochemical and physical manifestations of CPT II deficiency (Bonnefont et al. 2010). Valproic acid can trigger acute rhabdomyolysis in CPT II deficiency (Kottlors et al. 2001).

**OTHER DEFECTS OF LIPID METABOLISM**

Defects of mitochondrial (beta) oxidation are clinically heterogeneous but myopathic presentations occur in older children and adults (Laforet and Vianey-Saban 2010). Recurrent myalgia, rhabdomyolysis and myoglobinuria precipitated by
Chapter 26 Muscle Disorders

exercise and fasting may occur in very long chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency (Andresen et al. 1999). Short chain acyl-coenzyme A dehydrogenase (SCAD) usually presents in the first few months of life with a lipid storage myopathy, failure to thrive, hypotonia as well as seizures and may later cause a minicore myopathy with progressive external ophthalmoplegia (Tein et al. 1999). Other lipid storage myopathies presenting in childhood include multiple acyl-CoA-dehydrogenase defect (glutaric aciduria type II) (Olsen et al. 2004; Domizio et al. 2005) and long-chain 3-hydroxyacyl-CoA dehydrogenase (trifunctional protein) deficiency (Korenke et al. 2003; Tein 2013).

The management of patients with disorders of lipid metabolism is discussed in Chapter 9.

MITOCHONDRIAL MYOPATHIES

Mitochondrial cytopathies are relatively rare but within this group of disorders involvement of the CNS and neuromuscular system is common (Thorburn 2004; Di Mauro et al. 2013). The distinction between purely myopathic and more complex forms is to some extent artificial because of the ubiquitous cellular presence of mitochondria. Skewed heteroplasmy, whereby skeletal muscle might have a predominance of pathogenic mitochondrial mutations compared to other tissues, may account for apparent preferential muscle tissue involvement in some conditions.

Clinical Features

Mitochondrial myopathies may present from birth to adulthood and are extremely variable in their symptoms, severity and outcome (DiMauro et al. 2013). Some are part of complex encephalomyopathies while others are purely or essentially limited to skeletal muscle. If the presentation is that of a clinically pure myopathic process with predominantly proximal muscle weakness then symptoms such as fatigue, myalgia, exercise intolerance and episodic exercise-related myoglobinuria, although not diagnostic, give a clue to the myopathy being due to a metabolic condition. Ptosis and progressive external ophthalmoplegia are highly important clues (Moraes et al. 1989), as are other deficits such as such as cardiomyopathy, cognitive deficits, deafness, retinitis pigmentosa, ataxia and seizures. Like other inborn errors of metabolism, mitochondrial conditions may present during times of physiological stress, such as intercurrent illnesses, surgery or anaesthesia.

Investigation

If an obvious syndrome is not recognised clinically then early clues to a respiratory chain defect come from an elevated blood or CSF lactate or imaging abnormalities in the basal ganglia (Jackson et al. 1995). In some recognisable mitochondrial syndromes (e.g. MELAS, MERRF, NARP) mutations may be found in circulating lymphocytes, thereby avoiding the need for a biopsy (Taylor et al. 2004).

Even in the absence of significant weakness, histological and histochemical assessment of muscle tissue often gives the initial or the confirmatory clue to a mitochondrial disorder. The characteristic morphological abnormality, seen best on staining with Gomori trichrome, is the so-called ‘ragged red fibre’ due to accumulation of subsarcolemmal mitochondria. Electron microscopy may show abnormal mitochondrial structures which may contain paracrystalline inclusions (Fig. 26.3), with further assessment involving histochemical staining for the enzymes succinate dehydrogenase (SDH) which demonstrate mitochondrial proliferation and cytochrome c oxidase (COX). COX is encoded for by both nuclear as well as mitochondrial DNA (mtDNA) and a mosaic pattern of reactivity suggests a heteroplasmic mtDNA disorder, while an overall decrease suggests a nuclear DNA mutation (Taylor et al. 2004). Ragged red fibres are usually COX-negative but they can also be COX-positive (Taylor et al. 2004; DiMauro and Hirano 2005). An excess of lipids or glycogen is seen in some individuals affected by mitochondrial myopathy while, biochemical analysis of respiratory chain complex activity can point to defects in a single respiratory chain complex or multiple complexes. Further delineation is undertaken by molecular genetic studies of both mitochondrial (mt) and nuclear DNA (DiMauro and Hirano 2005).

Figure 26.3 Ragged red fibres in a case of Kearns–Sayre syndrome. Note subsarcolemmal deposits of red material representing mitochondria in most affected fibres while similar but less marked changes are beginning to appear in other fibres. (Courtesy Prof. B Lake, Great Ormond Street Hospital, London.)

CLINICAL MYOPATHIC SYNDROMES

Marked clinical heterogeneity, lack of phenotype–genotype correlations and the multisystem nature of mitochondrial disorders have meant that while a number of encephalopathic syndromes that involve muscle have been defined (e.g. MERRF, MELAS), there are very few predominantly or entirely myopathic phenotypes. Some exceptions are discussed below.
Cytochrome C Oxidase Deficiency

Cytochrome C Oxidase (COX) deficiency may present with severe congenital lactic acidosis, weakness and hypotonia which can be isolated or associated with renal and/or cardiac involvement. Infants become symptomatic before 3 months of age; weakness is usually progressive and fatal (Zeviani et al. 1985; Darin et al. 2003). A reversible form of COX deficiency presenting in the newborn period with severe weakness, ptosis, areflexia, increased creatine kinase and lactic acidosis relates to transient impairment of mitochondrial translation (Horvath et al. 2009; Mimaki et al. 2010; Uusimaa et al. 2011).

Coenzyme Q10 Deficiency

Deficiency of coenzyme Q10 (ubiquinone) presents in infancy as a multisystem disorder with encephalopathy, ataxia, nephropathy and myopathy (Trevisson et al. 2011). Later-onset cases have a myopathic presentation with exercise intolerance, progressive proximal muscle weakness and exercise-related myoglobinuria which may be associated with seizures, neuropathy and/or ataxia (Gempel et al. 2007). This disorder is important to recognise because it is potentially treatable with coenzyme Q10 replacement (Trevisson et al. 2011).

Mitochondrial DNA Depletion Syndromes

The mitochondrial depletion syndromes are often multisystemic but can be tissue specific. The myopathic form presents in infancy or early childhood with progressive weakness, hypotonia, areflexia, early onset of respiratory failure and death in the first decade (Martin-Hernandez 2016). Mutations in the thymidine kinase 2 (TK2) gene cause severe generalised muscle weakness which presents as a dystrophic condition in early infancy (Chanoprasert et al. 2013). Mutations in the SUCLA2 gene are also associated with mitochondrial DNA depletion and progressive muscle weakness, often with prominent multisystem features (Ostergaard et al. 2007).

Other Mitochondrial Myopathies

Development of sideroblastic anaemia during adolescence may give a clue to the syndrome entitled myopathy and sideroblastic anaemia (MLASA), which commences with exercise intolerance during childhood. Mutations have been found in the pseudo-uridine synthase 1 (PUS1) gene (Bykhovskaya et al. 2004). Childhood-onset exercise intolerance is also a prominent early feature resulting from mutations in the ANT1, Twinkle and POLG1 genes which cause defects in intergenomic signalling leading to multiple secondary mitochondrial DNA deletions (Trevisson et al. 2011; Mancuso et al. 2015).

Chronic Progressive External Ophthalmoplegia and Kearns-Sayre Syndrome

Chronic progressive external ophthalmoplegia (CPEO) usually presents in mid-adulthood with prosis and slowly progressive weakness of the extraocular muscles however occasionally presents in childhood, with diplopia usually absent or minimal. The differential diagnosis of CPEO includes myasthenia gravis and congenital fibrosis of the extraocular muscles (Schoer and Pongratz 2006).

Kearns-Sayre syndrome (KSS) is defined by the combination of CPEO and pigmentary retinopathy, often with short stature, ataxia, cardiac conduction defects, deafness, and cognitive deficits. KSS presents before age 20 years and progresses in adulthood (Yamashita et al. 2008).

Both CPEO and KSS can be caused by defects of mitochondrial or nuclear DNA and can occur sporadically or may be inherited in maternal, autosomal dominant or autosomal recessive patterns (di Mauro et al. 2013). Autosomal dominant and autosomal recessive forms of CPEO are linked to mutations in several nuclear DNA genes including POLG, C10orf2, RRM2B, SLCA25A4, POLG2, DGUOK and SPG7 which cause defects in intergenicomic signalling leading to multiple secondary mitochondrial DNA deletions (Yamashita et al. 2008; Mancuso et al. 2015).

Systemic Myopathies of Childhood

A number of systemic conditions can cause myopathies in childhood. These include endocrinopathies, renal conditions, infections, connective tissue disorders and eosinophilic syndromes.

Hyperthyroidism

Hyperthyroidism can cause a proximally-predominant pattern of muscle weakness in children, with respiratory and bulbar muscles usually spared. Ocular findings may include lid oedema, lid lag and proptosis with eye movements usually normal (Chan et al. 2002). The serum creatine kinase is not elevated and muscle biopsy shows non-specific abnormalities with atrophy of both type I and type II fibres. Neuroimaging shows enlarged extraocular muscles (Liu et al. 1996).

The incidence of myasthenia is increased in patients with hyperthyroidism and both hyperthyroidism as well as hypothyroidism can aggravate myasthenic weakness. Thyrotoxic
periodic paralysis can develop in adolescents and young adults usually of Asian or Latin American ethnicity and has been linked to susceptibility loci involving genes for muscle potassium channels (Ryan et al. 2010; Cheung et al. 2012). Treatment of these conditions is of the underlying thyrotoxicosis.

HYPOTHYROIDISM

More than a third of adults with hypothyroidism have muscle weakness and cramps with abnormal deep tendon reflexes (Duyff et al. 2000) but the figure for children is not clear: the degree of muscle weakness generally parallels that of the underlying hypothyroidism while the serum creatine kinase is moderately elevated. Where undertaken, muscle biopsy shows type 1 fibre predominance with selective type II atrophy.

In children with congenital hypothyroidism, muscle weakness and hypertrophy may produce a Herculean appearance which, in combination with a coarse facies, glossomegaly, hoarse cry and abdominal distention, is known as the Kocher–Debré–Sémélaigne syndrome (Agrawal and Thakur 2010): all symptoms resolve with treatment of hypothyroidism. This syndrome is exceedingly rare where neonatal thyroid screening programmes are in place. In older children and adults muscle hypertrophy very uncommonly develops with hypothyroidism, a phenomenon known as Hoffmann syndrome.

CUSHING SYNDROME

Cushing syndrome and exogenous steroid treatment give rise to a similar myopathic syndrome with progressive weakness, chiefly affecting the pelvic girdle, muscle wasting and sometimes pain. The EMG is myopathic but the serum creatine kinase, AST and ALT are normal while muscle biopsy shows selective atrophy of type II fibres. The myopathy resolves on treatment of the Cushing syndrome or on withdrawal or reduction of the steroid dose (Minetto et al. 2011).

CRITICAL ILLNESS NEUROPATHY/ MYOPATHY

A systematic study of 830 admissions to a paediatric intensive care unit for longer than 24 hours found that 1.7% developed generalised weakness (Banwell et al. 2003). Acute weakness in an ICU setting can be due to peripheral nerve, neuromuscular junction, muscle or combined aetiologies. Critical illness myopathy (CIM), sometimes known as acute quadriplegic myopathy, was initially described in patients with status asthmaticus receiving high-dose steroid therapy with or without associated nondepolarising blocking agents: other associations are with sepsis, multi-organ failure and organ transplantation (Williams et al. 2007). Serial creatine kinase monitoring may warn of an evolving myopathy (Tabarki et al. 2002) while in CIM affected muscles are electrically inexcitable (Rich et al. 1996). There is no specific treatment and recovery can be slow (Banwell et al. 2003).

MYOPATHIES ASSOCIATED WITH OTHER SYSTEMIC ILLNESSES

Muscle weakness and hypotonia are common features of rickets and osteomalacia. In some children they may be the presenting manifestation of this condition, causing diagnostic difficulty if bone X-rays are not obtained (Torres et al. 1986; van der Heyden et al. 2004; Alyaarubi and Rodd 2005). Phosphate depletion (Goodman et al. 1978), magnesium deficiency (Berkelhammer and Bear 1985) and hypermagnesaemia (Emser 1982) are rare causes of myopathy, as is parathyroid disease. Muscle weakness may also be seen in malnourished children (Donley and Evans 1989; Renault and Quesada 1993) although the respective roles of neural and muscular involvement are unclear.

Drug side-effects must always be considered in a child presenting with weakness or rhabdomyolysis but in practice this is a rare issue in children. Medication-related myopathies can be seen with treatment with procainamide (Lewis et al. 1985), sodium valproate (Kasturi and Sawant 2005), clofibrate, labetolol, statins and didanosine (Vladutiu 2008). Hypokalaemia can cause a myopathy after treatment with cisplatin and amphotericin B (Mohammadianpanah et al. 2004).

ARTHROGRYPOSIS MULTIPLEX CONGENITA AND AKINESIA DEFORMATION SYNDROME (MULTIPLE CONGENITAL CONTRACTURES)

Congenital contractures can be isolated or can affect multiple joints. The term arthrogryposis multiplex congenita (AMC) describes a heterogeneous group of disorders whose common feature is congenital contractures of several joints. Arthrogryposis is a clinical finding rather than a specific diagnosis and is seen in more than 300 specific conditions (Hall 1997): in many affected individuals the aetiology remains unknown. Arthrogryposis affects one in 3000 live births (Fahy and Hall 1990). Fetal movement is required for normal joint development and a common factor to all syndromes associated with multiple congenital contractures is reduced or absent fetal movements. The term fetal akinesia deformation syndrome (FADS) is now applied to the series of phenotypes resulting from reduced movement in utero. Common features of FADS, in addition to joint contractures, include craniofacial changes, micrognathia, limb pterygia, pulmonary hypoplasia and intrauterine growth retardation. FADS may result from any cause of reduced movement including exogenous factors (e.g. maternal anti-acetylcholine receptor antibodies), restricted fetal environment (e.g. oligohydramnios), and disorders of the central nervous system or peripheral neuromuscular system. The clinical presentation and outlook of these conditions is very variable, depending on the timing of
the period of immobility, the number and location of immo-
bilised joints as well as the presence or absence of brain and
other abnormalities.

In evaluating an infant with AMC it is important to
undertake a detailed neurological examination. A normal
neurological examination suggests arthrogryposis is due to
amyoplasia, distal arthrogryposis, a generalised connective
tissue disorder or fetal crowding. In contrast, weakness and
abnormalities of the deep tendon reflexes suggest that move-
ment was decreased in utero as a result of an abnormality of
the central or peripheral nervous system, the motor end plate
or muscle.

AMYOPLASIA CONGENITA

Amyoplasia congenita, the most common form of FADS, is
associated with a distinctive pattern of joint contractures (Hall
et al. 2014) while amyoplasia occurs sporadically. In most but
not all individuals affected there is symmetrical involvement
of all four limbs with reduced muscle mass, internal rotation
of the arms, sloping of the shoulders, extension of elbows,
flexion of the wrists, flexed fingers, flexion of the hips and
knees, as well as usually severe equinovarus deformities of the
feet (Fig. 26.4). A minority of individuals have contractures
involving only three limbs, only the upper limbs or only the
lower extremities (Hall et al. 2014): there may also be asso-
ciated gastro-intestinal anomalies, congenital absence of dig-
its and congenital fractures (Hall et al. 2014). Amyoplasia is
thought to result from vascular compromise in utero or may
be neurogenic in origin.

Fetal movements are usually reported to be reduced, breech
presentation is common and delivery is often by caesarean sec-
tion. Fractures at birth are common (Sells et al. 1996) while
the hips may be subluxed or dislocated. Joint contractures are
associated with shortening of the limbs and dimples over the
joints with loss of the deep tendon reflexes but normal sen-
sation. A flat capillary angioma – usually midline facial but
occasionally located elsewhere – is present in 80–90% of indi-
viduals affected (Sells et al. 1996). Micrognathia is common
and about one in four of affected infants have contractures
of the temporo-mandibular joint. Feeding difficulties are very
common in infancy and may be followed by language prob-
lems as well as poor growth. Intelligence is usually normal.

Pathologically, the anterior horns have reduced numbers
of large motor neurons with only minimal gliosis and the
smaller anterior horn neurons are present or increased
(Hageman et al. 1987), with the muscles having fibro-fatty
tissue interspersed with normal–looking muscle fibres. The
EMG may show mild signs of denervation, suggesting a
longstanding loss of some motor nerve fibres.

Early specialist physiotherapy intervention, early surgery,
rehabilitation and careful follow-up are essential to give opti-
mum results (Mennen et al. 2005): the outcome is relatively
good despite the extensive deformities. Of 38 children studied
by Sells et al. (1996), two thirds were fully ambulant by 5 years
of age and most were completely or relatively independent.
Most had undergone numerous orthopaedic procedures,
including castings.

DISTAL ARTHROGRYPOSIS

The distal arthrogryposis syndromes affect predominantly the
hands and feet, are often associated with an abnormal facies
and almost always dominantly inherited, although possibly
with reduced penetrance and variable expressivity (Bamshad
et al. 1996; Beals 2005). Nine subgroups have been identified,
of which at least five have a known genetic basis. Characteristic findings in these subgroups include:

Type 1 Camptodactryly, talipes equinovarus foot deformities, normal facies
Type 2 Freeman–Sheldon syndrome: contractures of hands and feet, characteristic (‘whistling’) facies, flexion and ulnar deviation of the fingers, scoliosis
Type 3 Gordon syndrome: cleft palate, finger contractures, short stature
Type 4 Scoliosis, finger contractures
Type 5 Finger contractures, ptosis, restricted eye movements, strabismus
Type 6 Finger contractures, sensorineural hearing loss
Type 7 Temporomandibular contractures, camptodactyly
Type 8 Finger contractures, multiple pterygia with stunted growth
Type 9 Beals syndrome: finger contractures, ear deformity

Common deformities in the upper limbs include ulnar deviation, camptodactyly, hypoplastic and/or absent flexion creases and overriding fingers, while in the legs common features include talipes equinovarus, calcaneovalgus, vertical talus and metatarsus varus (Beals 2005). Most of the distal arthrogryposis syndromes spare the proximal joints.

A vast number of complex syndromes of chromosomal or genetic origin featuring multiple congenital contractures, dysmorphism and multisystem abnormalities also underlie FADS (Ravenscroft et al. 2011; Hall 2014). The most common is the Pena–Shokeir phenotype (Pena and Shokeir 1974; Hall 2009) which includes intra-uterine growth retardation, craniofacial anomalies, limb contractures and a variety of other anomalies including pulmonary hypoplasia and short gut. At least 20 familial forms are recognised but peripheral neuromuscular disorders can also underlie the Pena–Shokeir phenotype (Hall 2009).

**CENTRAL NERVOUS SYSTEM CAUSES OF ARTHROGRYPOSIS**

Developmental abnormalities of the brain, either genetic, or caused by infection or vascular lesions, are sometimes associated with arthrogryposis: such conditions may be associated with increased tone and spasticity. Chromosomal anomalies are a rare cause of AMC, while arthrogryposis is sometimes seen in children with congenital forms of spinal muscular atrophy, such as those associated with mutations in *UBE1* (Ramser et al. 2008).

**ARTHROGRYPOSIS DUE TO MUSCLE AND NERVE DISEASES**

Arthrogryposis is relatively common in severe neuromuscular disorders associated with fetal akinesia. The molecular basis of individuals affected by this condition is extremely varied but much easier to identify with the advent of next-generation sequencing techniques allowing rapid and affordable screening for large numbers of conditions (Ravenscroft et al. 2011). Myopathies and muscular dystrophies are more commonly implicated than congenital neuropathies.

A very rare but important cause of FADS is transient neonatal myasthenia gravis caused by transplacental passage of maternal anti-acetylcholine receptor antibodies. Transient neonatal myasthenia gravis usually remits spontaneously over days to weeks after delivery but occasionally persists, leaving the child with multiple joint contractures (AMC) or a fixed myopathy, often with marked dysarthria and velopharyngeal incompetence. FADS with congenital contractures is more often seen in children with maternal antibodies directed against fetal acetylcholine receptors. Although rare this is an important cause to recognise not only because of the recurrence risk but also as it is potentially treatable (Hacohen et al. 2014).

**OTHER MUSCLE ABNORMALITIES**

**CONGENITAL AGENESIS/HYPOPLASIA**

Congenital agenesis or hypoplasia of muscle is common and may involve a whole muscle or parts of various muscles including (in decreasing order of frequency) the pectoralis, trapezius, sternocleidomastoid, serratus anterior and quadriceps femori. One common condition is the Poland syndrome in which absence or hypoplasia of the pectoral muscles is variably associated with ipsilateral thoracic and upper limb anomalies (Yiyit et al. 2015): focal agenesis of muscles is usually asymptomatic while vascular abnormalities may be a cause in some patients (Lee et al. 1995). The prune belly syndrome is characterised by absence or hypoplasia of abdominal wall muscles (Hassett et al. 2012). Thenar hypoplasia (Cavanagh syndrome) may be either unilateral or bilateral and can be associated with cardiac or ocular anomalies (Sonel et al. 2002).

**CONGENITAL MUSCULAR TORTICOLLIS**

Congenital muscular torticollis is a musculoskeletal deformity usually apparent in the first month of life and characterised by persistent head tilt towards the affected side, with the chin rotated towards the opposite side. Torticollis can be purely postural, a preferred position for the infant with no restriction of movement of the sternocleidomastoid muscle, or associated with shortening of the sternocleidomastoid muscle, or without a palpable sternocleidomastoid mass (or ‘tumour’) (Cheng et al. 2000). Aetiology is poorly understood but may
relate to malpositioning in utero; occasional instances where this is inherited are described (Engin et al. 1997; Hosalkar et al. 2001). Presence of other findings such as plagiocephaly, craniofacial asymmetry or cranial nerve abnormalities should prompt specialist assessment. Treatment consists of gentle passive stretching and avoidance of factors promoting asymmetry (such as lack of prone positioning, excessive time in car seats and persistence of single positions in bed or during feeds). Rare treatment-refractory patients require surgical release (Cheng et al. 2000).

**MUSCLE HYPERTROPHY**

Generalised or focal muscle hypertrophy may be caused by many myopathic or neurogenic disorders. While the dystrophinopathies and other muscular dystrophies are the most common causes of muscle hypertrophy, this finding can also be seen in hypothyroidism (Kocher–Debré–Sémélaigne and Hoffmann syndromes) and myotonia congenita. Extraordinary hypertrophy has been described in a child with a mutation in the myostatin gene (Schuelke et al. 2004).

**MYASTHENIA AND DISORDERS OF THE NEUROMUSCULAR JUNCTION**

Diseases of the neuromuscular junction are clinically characterised by weakness and increased muscular fatigability. This group of conditions includes autoimmune diseases, congenital myasthenic syndromes and forms of neuromuscular blockade due to drugs, toxins or other exogenous factors. Infant botulism is discussed in Chapter 11.

**Myasthenia Gravis**

Myasthenia gravis is a rare auto-immune condition caused by autoantibodies directed against protein components of the neuromuscular junction. Myasthenia gravis presenting in childhood is classified either as transient neonatal myasthenia gravis (very rare, from transplacental transfer of maternal antibodies) or juvenile myasthenia gravis (more common, resulting from autoantibodies). About 10% of individuals affected by myasthenia gravis are children.

Myasthenia gravis is usually caused by antibodies to acetylcholine receptors (AChR) on the postsynaptic membrane of skeletal muscle. These antibodies bind to the acetylcholine receptor, activating the complement cascade and causing destruction of the postsynaptic membrane and loss of functional acetylcholine receptors at the postsynaptic membrane (Andrews et al. 1993). Anti-acetylcholine receptor antibodies are sometimes not identifiable in juvenile myasthenia gravis this is described as ‘sero-negative’ myasthenia gravis although other antibodies may be detectable. Sero-negative myasthenia gravis may be linked to antibodies to muscle-specific kinase (MuSK), a receptor tyrosine kinase which acts as an essential component of the developing neuromuscular junction (Koneczny et al. 2014). Other antibodies of uncertain significance may also be present in juvenile myasthenia gravis; these may include those directed against titin, the ryanodine receptor LRPL4 and the intracellular AChR-associated protein, rapsyn (Vincent et al. 2012).

The mechanism responsible for the production of these autoantibodies is unknown. A role of the thymus is suggested by the association of AChR-myasthenia gravis with thymic lymphoid hyperplasia and tumours as well as by the effects of thymectomy. Thymic histology, if abnormal, is only minimally so in anti-MuSK myasthenia gravis (Berrih-Aknin and Le Panse 2014). A genetic susceptibility is suggested by the relative frequency of clinical or EMG manifestations in relatives of individuals with myasthenia and by increased frequency of some HLA groups (Kerzin-Storrar et al. 1988). Other auto-immune disorders may cosegregate with myasthenia gravis, particularly thyroid disease (hyper- or hypothyroidism), rheumatoid arthritis, lupus erythematosus and diabetes (Yeh et al. 2015).

**Clinical features of myasthenia gravis**

Symptoms may occur any time after one year of age but the disease is most prevalent in adolescent girls (Andrews et al. 1994). Virtually all children with myasthenia gravis have ocular involvement (variable ptosis, diplopia and/or ophthalmoplegia) at presentation, which is variably associated with symptomatic bulbar (dysphagia, dysarthria and hypernasality) and proximal limb involvement. In a proportion of these individuals (20–50%, and up to 80% in young Chinese children) (Wong et al. 1992; Afifi and Bell 1993; Anlar et al. 2005) muscle weakness remains confined to the ocular muscles; pure ocular myasthenia is more common in children than adults and usually seen prepubertally. Involvement of muscles other than those around the eyes (‘generalised myasthenia’), usually evolves within two years of initial ocular symptoms and is more common in postpubertal adolescents.

A characteristic finding in myasthenia gravis is fatigability; variability in muscle function with good strength after rest and deterioration following exercise or towards the end of the day. This history of fatigue is occasionally either absent or difficult to obtain.

Ocular signs in myasthenia gravis may be symmetrical, asymmetrical or unilateral (Afifi and Bell 1993) and more easily seen on sustained upgaze. There is often weakness of the facial muscles, particularly the orbicularis oculi and neck flexors, while proximal limb muscle weakness may be present at the outset or develop later. Fatigability may be brought out by repeated testing of muscle groups, that is, by repeated shoulder abduction or squats. The deep tendon reflexes are normal and there are no sensory deficits.

Anti-MuSK-myasthenia gravis is rare in children but has been reported as early as 14 months of age (Yilmaz et al. 2014) and may be more common in females. In adults the clinical picture of anti-MuSK myasthenia gravis is dominated by
cranial and bulbar muscle weakness as well as frequent episodes of respiratory crises (Evoli et al. 2003) but it is not clear whether anti-MuSK-Myasthenia gravis and anti-AChR-Myasthenia gravis differ significantly in childhood.

The natural course of JMG is variable: in the absence of treatment it tends to be slowly progressive with fluctuations on a baseline of reduced function. ‘Myasthenic crises’ with increased weakness and involvement of the respiratory muscles may occur spontaneously or following febrile illnesses and may require emergent management as well as assisted ventilation.

The differential diagnosis of juvenile myasthenia includes other neuromuscular disorders in which fatigability can sometimes be marked, such as myopathies and congenital myasthenic syndromes as well as mitochondrial disorders and botulism. Rare myasthenic syndromes result from the use of agents such as penicillamine, carnitine and aminoglycosides. Structural lesions of the midbrain, such as tumours, may cause fatigable ptosis, ophthalmoplegia and oropharyngeal weakness, mimicking myasthenia. Imaging studies should be performed if the diagnosis of myasthenia gravis is not definitive, particularly if signs are confined to the cranial nerve territories.

**Diagnosis of Myasthenia Gravis**

The diagnosis of juvenile myasthenia gravis (JMG) is primarily a clinical one but a number of tests provide useful supportive data. These tests have variable sensitivity, especially in children with ocular myasthenia gravis.

Antibody testing for anti-AChR antibodies or in their absence anti-MuSK antibodies is relatively inexpensive and straightforward. A positive acetylcholine antibody test is essentially diagnostic in the appropriate clinical setting with false positives very rare. Anti-AChR antibodies are more likely to be present in children with generalised myasthenia gravis than in pure ocular myasthenia gravis. Anti-AChR antibodies can be found in only 50% of prepubertal children, but are seen in 60–80% of postpubertal children with myasthenia gravis (Afifi and Bell 1993; Andrews et al. 1993). Of those seronegative for AChR antibodies about 40–50% are seropositive for anti-MuSK antibodies (MuSK-myasthenia gravis) (Evoli et al. 2003; Vincent and Leite 2005). The antibody titre does not vary with disease severity or after thymectomy in anti-AChR myasthenia gravis (Anlar et al. 2009; Yilmaz et al. 2015).
Administration of a short-acting anticholinesterase agent to demonstrate reversibility of ptosis, ophthalmoplegia or dysarthria is a useful adjunct investigation supporting the diagnosis of a myasthenic process. Edrophonium chloride given intravenously has a rapid onset of effect (30 seconds) with a short duration (5 minutes). The effect may be immediate and obvious but can be difficult to gauge in small children: assessing the response, particularly in young children, can be aided by taking photographs or (preferably) videotaping the procedure. Muscarinic side-effects of edrophonium and the related agent, neostigmine, include hypersalivation, bradycardia and asystole; these can be avoided by pre-treatment with intravenous atropine. The maximum dose of edrophonium chloride varies with age (1–10mg): a small test dose is usually given first, the rest being injected after 30–60 seconds if there is no response after the test dose. This test should always be performed with resuscitation equipment available. A negative anticholinesterase test does not exclude JMG and a positive result is sometimes only obtained on repeat testing. Conversely, a positive test is not pathognomonic and should not be the only basis for diagnosis (Drachman 1994).

Repetitive nerve stimulation (RNS) is a variant of motor nerve conduction testing. Serial compound muscle action potentials are recorded from surface electrodes placed over a weak muscle, with the nerve being stimulated at 2–3 Hz. A decrement in amplitude of more than 10% from the third to the fifth response is abnormal, providing evidence of a defect in neuromuscular junction transmission: this abnormality is corrected after injection of anticholinesterase. A normal RNS does not exclude JMG; in one series RNS was positive in only 33% of individuals when distal nerves were tested and in 66% when both proximal and distal nerves were tested (Afifi and Bell 1993). The test can be technically challenging and may be uncomfortable for children; it should only be undertaken by experienced neurophysiologists. Negative testing may prompt additional investigations such as high-frequency (20–50Hz) repetitive nerve stimulation, on which an increment in the size of the responses recorded may suggest a presynaptic neuromuscular junction transmission defect such as infant botulism or the Lambert-Eaton syndrome. Single-fibre EMG, which demonstrates increased ‘jitter’ in the latencies of two fibres of a single motor unit, is more sensitive than classic RNS in diagnosis of myasthenia gravis but difficult to perform in children (Pitt 2008).

Hyperthyroidism occurs in 3–8% of patients with JMG and either hyperthyroidism or hypothyroidism may aggravate myasthenic weakness. Thyroid function should be tested in all patients with suspected myasthenia gravis (Drachman 1994) and evidence for other autoimmune disorders should be sought by careful history, clinical examination as well as laboratory tests where indicated: JMG is rarely associated with thymoma (Ware et al. 2012; Castro et al. 2013). All children with generalised myasthenia gravis should undergo either chest CT or MRI to exclude a concomitant thymoma; imaging should also be considered in children with oculomotor myasthenia gravis, although their risk of thymoma is extremely low.

**Treatment of Myasthenia Gravis**

The aims of treatment of myasthenia gravis include enhancement of neuromuscular transmission with anticholinesterase agents and modulation of the abnormal immune activation causing this condition. Potential immunotherapeutic options include relatively short-acting treatments such as plasma exchange and intravenous immunoglobulin, longer-term agents such as prednisolone, cyclosporine and azathioprine as well as surgical thymectomy (Drachman 1994).

Rodriguez et al. (1983) observed spontaneous remissions in 30% of patients after a 15-year follow-up but in those with generalised weakness the remission rate was significantly lower. Younger patients are much more likely to grow into spontaneous remission than older children and adults. Prepubertal Caucasian children demonstrate a higher rate of spontaneous remission than African-American children, who also have a lower rate of response to thymectomy (Andrews et al. 1994).

Pre-adolescent children in whom the spontaneous remission rate is high and older children with purely ocular myasthenia can often be successfully managed with anticholinesterase agents alone: older children and adolescents require additional therapy directed against the immune system abnormality. The relative efficacy of these therapies in paediatric subgroups is difficult to determine given that this is a rare and clinically heterogeneous condition (Ware et al. 2012; Castro et al. 2013). The agents used are generally determined on an individual basis, based upon institutional experience and with the long-term cost–benefit ratio in mind (Richman and Agius 2003).

The aim of immunotherapy for myasthenia is to induce and then maintain immunological remission. Corticosteroids, sometimes used in combination with intravenous immunoglobulin or plasmapheresis, are effective for induction of remission. Maintenance of the remission with a slow reduction of the maintenance corticosteroid dose may be accomplished with other drugs such as azathioprine or by thymectomy (Richman and Agius 2003).

**Anticholinesterase agents**

Anticholinesterase agents are the first line of treatment of myasthenia but are symptomatic rather than curative. These drugs increase the half-life of acetylcholine released into the synaptic cleft by inhibiting hydrolysis by acetylcholinesterase, thus increasing the probability of acetylcholine molecules reaching the reduced number of receptors on the postsynaptic membrane (Drachman 1994); while an initial good response is usually seen, effectiveness may wane over time. Pyridostigmine is the most commonly used oral agent; neostigmine may be useful parenterally during crises or when oral intake is otherwise not possible. The clinical effect of pyridostigmine commences after about 30 minutes and peaks about 2 hours post-dose.
The initial dose of pyridostigmine is 0.5–1mg/kg every 4–6 hours, with a maximal dose of 7mg/kg/day. The dosage should be slowly increased with timing tailored to the individual needs of the child. In adolescents, doses greater than 120 mg given five times per day rarely give extra benefit and increase the risk of cholinergic crisis. The sustained-release preparation of pyridostigmine should be used only for troublesome symptoms overnight or on wakening, as there is evidence from animal studies that sustained exposure to anticholinesterase agents may damage the endplate region of the neuromuscular junction (Hudson et al. 1978). Parents should be counselled as to potential adverse effects of pyridostigmine, which include abdominal cramping and diarrhoea. Diaphoresis, nausea, vomiting, bradycardia and miosis are seen with significant over-treatment and may be complicated by increased muscle weakness, a ‘cholinergic crisis’. Treatment of cholinergic crisis is a reduction or cessation of pyridostigmine followed by a slow reintroduction once all symptoms have resolved.

Children with anti-MuSK myasthenia often respond relatively poorly to anticholinesterase therapy and may be at increased risk of cholinergic crisis (Ionita and Acsadi 2013).

**Corticosteroids**

Corticosteroids induce remission in most children with JMG but their long-term use should be based only on a considered decision taking into account the long-term side effects of corticosteroid therapy, including weight gain, growth suppression, osteoporosis, hypertension and susceptibility to infection (Ionita and Acsadi 2013). Initiation of high-dose corticosteroid therapy may cause increased weakness in children with myasthenia; a low starting dose (0.5mg/kg/day) is therefore required for outpatients, with a gradual increase over the following weeks. In children with severe weakness or those in myasthenic crisis higher doses may be given but inpatient monitoring of respiratory function is essential and additional treatment with intravenous immunoglobulin or plasmapheresis should be considered (Richman and Agius 2003). Once children are in remission, a prednisolone dose of 1–2mg/kg/day is given as maintenance until good disease control is sustained for some time, when a very slow steroid wean should be initiated. Switching to an alternate-day schedule may maintain remission while minimising side-effects.

**Intravenous Immunoglobulin**

Pooled immunoglobulin from blood donors can be given intravenously and is a safe and effective treatment of paediatric myasthenia gravis. (Selcen et al. 2000; Ionita and Acsadi 2013). Intravenous immunoglobulin (IVIG) is probably superior to plasma exchange in terms of ease of use and side-effect profile in children. IVIG may have a role for acute intervention in myasthenic crises or the acutely unwell, or as a chronic maintenance therapy when all other treatment modalities have failed (Ionita and Acsadi 2013). Benefit may be seen in 3 or 4 days but lasts less than 3 months. Possible side-effects include headaches, back pain and aseptic meningitis.

**Plasma Exchange**

Plasma exchange can produce rapid but short-lived improvement in myasthenia gravis and has been used for the treatment of myasthenic crises as well as for pre- and post-operative support. Plasmapheresis is rarely used as maintenance therapy for myasthenia as it requires two large-bore intravenous lines and benefits are only transient (Ionita and Acsadi 2013).

**Other Long-Term Immunotherapeutics**

Other long-term immunotherapies may be required as an alternative to corticosteroids or as a steroid-sparing strategy. Azathioprine may be used in conjunction with steroids or in isolation (Wäre et al. 2012). A randomised, double-blinded trial in adults showed that azathioprine, used as an adjunct to alternate-day prednisolone in antibody-positive generalised myasthenia gravis, reduced the maintenance dose of prednisolone and was associated with fewer treatment failures, longer remissions and fewer side effects (Palace et al. 1998). Testing of thiopurine methyltransferase activity and/or genetic variants in the TPMT gene is important prior to initiation of azathioprine therapy to enable accurate dosing calibration (Relling et al. 2011).

Cyclosporine, tacrolimus and mycophenolate mofetil can all be considered if azathioprine is not tolerated, while cyclophosphamide has been used for very severe disease (Richman and Agius 2003). High-dose pulse methylprednisolone has been used successfully in children with refractory disease (Sakano et al. 1989).

**Thymectomy**

Thymectomy is always indicated in children with thymomas. Thymoma is much less common in children than adults with myasthenia gravis. In those without thymoma thymectomy improves the chances of inducing a long-term remission in JMG, particularly in those who appear to have relatively treatment-refractory disease (Wäre et al. 2012). It is usually indicated for moderate or severe disease, particularly if there are oropharyngeal or respiratory symptoms. Intervention with short-term agents such as IVIG, plasma exchange or corticosteroids may be required for stabilisation before or after surgery. Thymectomy frequently results in significant and lasting improvement, although other long-term therapy remains necessary for some time as the full benefit of thymectomy may not be evident for a year or more. Children are more likely to be improved or go into remission if thymectomy is performed early, particularly within the first year following the onset of symptoms (Andrews et al. 1994; Richman and Agius 2003; Heng et al. 2014). Endoscopic thymectomy may yield excellent results but care must be taken that all thymic remnants are removed intra-operatively (Wäre et al. 2012; Christison-Lagay et al. 2013; Goldstein et al. 2015).

Adults with anti-MuSK myasthenia gravis, in which there is little or no thymic abnormality, do not respond to thymectomy (Evoli et al. 2003).
Wittbrodt (1997) reviewed drugs prescribed for coexisting conditions that may impair neuromuscular transmission. Commonly prescribed agents which may exacerbate symptoms in myasthenia gravis include aminoglycoside antibiotics, ciprofloxacin, lithium, penicillamine, magnesium and botulinum toxin.

**TRANSIENT NEONATAL MYASTHENIA**

Approximately 5–10% of infants born to mothers with myasthenia are affected by transient neonatal myasthenia gravis (NMG), after antibodies directed against acetylcholine receptors are transferred from the maternal to the fetal circulation (Hoff et al. 2003). In one study 13 of 30 newborn infants of myasthenic mothers were anti-AChR antibody positive: all five newborn infants clinically affected were in the AChR antibody-positive group and no AChR antibody-negative mothers had an affected infant (Batocchi et al. 1999).

Importantly, many patients with myasthenia gravis have antibodies directed not only against the main adult immunogenic region of the AChR but also against the fetal isoform (Polizzi et al. 2000). The adult: fetal antibody ratio has been found to predict, either before or during pregnancy, the occurrence of NMG for the first child at least (Gardnerova et al. 1997). There is no relation between the severity of maternal disease and involvement of the infant.

The clinical features of transient neonatal myasthenia are usually distinctive (Papazian 1992). The onset is delayed to a few hours after birth, sometimes as long as 2–3 days and is marked by hypotonia, feeding difficulties due to poor sucking and/or swallowing, poor crying and facial diplegia. Proptosis is present in only a minority of individuals while respiratory distress requiring mechanical ventilation may occur. These features permit an easy diagnosis when myasthenia is known in the mother but she may be undiagnosed or asymptomatic. The diagnosis may be suspected if there is a positive response to administration of anticholinesterases. Repetitive nerve stimulation can also be used to assist diagnosis but is painful and can be technically difficult in infants.

Treatment is with maintenance anticholinesterase therapy. In severe forms with respiratory distress and/or profound hypotonia exchange transfusion has been used (Pasternak et al. 1981). The role of IVIG is not clear (Bassan et al. 1998): symptoms usually resolve by 4–6 weeks but occasionally can take up to several months (Morel et al. 1988).

More severe, less common variants of neonatal myasthenia gravis include the fetal akinesia deformation sequence (FADS) and the fetal acetylcholine inactivation syndrome. FADSs in infants of myasthenic mothers is characterised by a combination of fixed joint contractures and craniofacial anomalies (hypertelorism, micrognathia, low-set ears), limb anomalies as well as pulmonary hypoplasia (Polizzi et al. 2000). The fetal acetylcholine receptor inactivation syndrome presents in the neonatal period with facial diplegia, a high arched palate, velopharyngeal incompetence, conductive hearing loss and cryptorchidism (Oskoui et al. 2008; Hacohen et al. 2014). Antibodies against the AChR are markedly elevated, although not always specific for the fetal AChR subunit (Hacohen et al. 2014). Muscle weakness may be significant and permanent but may respond to some degree to treatment with salbutamol (Allen et al. 2016).

**CONGENITAL MYASTHENIC SYNDROMES**

The congenital myasthenic syndromes (CMS) are a heterogeneous group of genetic disorders of neuromuscular transmission. Anatomically, CMS generally arise from molecular defects of neuromuscular junction proteins at the presynaptic, synaptic or postsynaptic levels. With the advent of whole exome sequencing, more than 20 individual CMS are now recognised (Table 26.6) (Engel et al. 2015).

Most individuals display symptoms in the newborn period or the first year or two of life however these can occasionally present in later childhood or even adulthood and may be misdiagnosed as congenital myopathies or seronegative autoimmune myasthenia gravis (Burke et al. 2004). Autosomal recessive inheritance is seen in all but the slow channel syndrome and synaptotagmin 2 deficiency (Herrmann et al. 2014).

The clinical picture is variable. There is often an obstetric history of reduced fetal movement, polyhydramnios and preterm delivery, or congenital joint contractures may be present. Feeding difficulties with poor suck and cry, ptosis and ophthalmoplegia, as well as facial and generalised weakness often dominate the neonatal period: mild facial dysmorphism and a high-arched palate are also reported (Goldhammer et al. 1990; Burke et al. 2004). Later, delay in motor milestones, fluctuating proptosis and ophthalmoplegia, oropharyngeal dysfunction as well as weakness and fatigability are common (Engel et al. 2015). Life-threatening episodes of respiratory insufficiency with sudden apnoea and cyanosis can be seen from birth or later in infancy. These episodes are often precipitated by minor infections or other intercurrent illnesses and can point to the myasthenic syndromes caused by choline acetyltransferase deficiency, rapsyn mutations and sodium channel mutations (Engel et al. 2015).

Diagnosis is based on the nerve conduction studies, which generally show a decremental response to repetitive nerve stimulation or increased jitter on single-fibre EMG. Empiric trials of treatment with anticholinesterase and 3–4 diaminopyridine (which increases acetylcholine quantal release) may give a guide to the underlying diagnosis but can lead to an increase in weakness in some rare forms (such as, e.g. COLQ deficiency) and are only recommended in hospital settings with access to emergency care. Ephedrine and salbutamol help in other individuals (Beeson et al. 2005). Genetic testing for the known various CMS is now commercially available.
LAMBERT–EATON MYASTHENIA SYNDROME

Lambert–Eaton myasthenia syndrome (LEMS) is a very rare immune-mediated disorder of presynaptic neuromuscular junction transmission. LEMS is clinically characterised by fatigable muscle weakness, hyporeflexia and autonomic disturbance: it is much more common in adults in whom it is associated with antibodies to presynaptic voltage-gated calcium channels. About half of the adults with this condition have an associated small-cell lung carcinoma (SCLC) which also expresses these calcium channels (Titulaer et al. 2011). Neoplasms associated with paediatric LEMS include leukaemia, neuroblastoma, Burkitt lymphoma and Wilms’ tumour (reviewed by Hajjar et al. 2014).

The diagnosis is suggested by neurophysiological studies which show low-amplitude CMAPs with marked facilitation on high-frequency repetitive nerve stimulation (Hajjar et al. 2014). Treatment is of the underlying malignancy where present and by immunosuppression, pyridostimine and 3, 4 DAP.

Other Neuromuscular Blocking Agents

Drugs potentially interfering with neuromuscular transmission are discussed above in the section on Juvenile Myasthenia Gravis. This topic has been reviewed by Witthördt (1997). The toxins of several venomous animals have been instrumental in understanding the structure and function of the neuromuscular junction (Vincent et al. 2000). Agents impairing neuromuscular transmission at a presynaptic level include arthropod venoms and some insect bites, while several snake venoms are active at the postsynaptic level (Kularatne and Sananayake 2014). Electrophysiological abnormalities are also an indication of acetylcholinesterase inhibition secondary to organophosphate poisoning (Besser et al. 1989).

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Electrolyte and Acid-Base Metabolism Disturbances, Nutritional Disorders and Other Systemic Diseases

Peter Baxter

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A degree of neurological involvement is common in many systemic diseases, some of which have already been discussed or alluded to elsewhere in this book. Such involvement represents a significant part of the work of neurologists and serves to remind us that the nervous system is critically dependent on the rest of the organism. A complete coverage of this vast field is not the aim of this chapter, which is limited to the most important disorders that can produce major neurological disturbances and which have not been previously dealt with. These include neurological syndromes due to disturbances of the electrolyte and acid-base metabolism to which the nervous system is extremely sensitive, nutritional diseases involving the central nervous system (CNS), which represent a major cause of neurological disease in developing countries, and CNS involvement in endocrine and visceral diseases. Both the peripheral and the CNS can be affected in several of these conditions (Aicardi 2009a).

**DISORDERS OF WATER AND ELECTROLYTE METABOLISM**

**COMPLICATIONS OF ACUTE DEHYDRATION**

Globally, acute dehydration is one of the commonest preventable causes of death and morbidity in childhood. Younger children, especially infants, and those with pre-existing problems such as undernutrition, are at particular risk. Gastroenteritis is well recognised as the most common cause, but dehydration can also follow insufficient intake, or water loss due to other gastrointestinal disorders, excess diuresis or excess sweating. Evidence-based guidelines are widely available for the assessment and management of acute gastroenteritis and of dehydration, but compliance by health professionals may still vary (Kosek et al. 2003; NICE 2009; Niescierenko and Bachur 2013; Freedman et al. 2015).

As well as systemic features, early neurological symptoms of hypovolaemia include headache and pre-syncopal features such as orthostatic dizziness, which are difficult to assess in young children. Later ones include irritability, fatigue, lethargy and muscle cramps, while a reduced conscious level is a near terminal sign of severe shock (NICE 2009).

Hypovolaemia from any cause is a significant risk factor for acute venous stroke, especially when exacerbated by sepsis or haematological risk factors. The latter include anaemia, polycythaemia, thrombocytosis, haemoglobinopathies and prothrombotic conditions. Hypovolaemia and haemoconcentration secondary to nephrosis are also recognised predisposing factors. As well as focal deficits, presenting features of venous stroke can include seizures and encephalopathy. Complications include hydrocephalus and subdural, subarachnoid or intracerebral haemorrhage. The diagnosis is confirmed by neuroimaging. The presenting features and management of acute venous stroke are discussed in Chapter 15.

The role of hypovolaemia in the aetiology of acute arterial ischaemic stroke is less marked, but correction of fluid and electrolyte imbalances is also part of standard acute management.

Hypovolaemia and vascular collapse following acute blood loss, vasodilatation, or capillary leak, including septic shock and post-traumatic states, carry similar neurological risks. If complicated by disseminated intravascular coagulation there is additional risk of haemorrhage. In a large African study of children with infection and shock, in the acute phase 15% were in coma and 37% had seizures; 2% of survivors had neurological sequelae.

Hypovolaemia and electrolyte disturbance are also recognised complications of therapeutic hypothermia, but their contribution to any long-term sequelae is difficult to disentangle from those caused by the primary pathology (Roach et al. 2008; Polderman 2009; Maitland et al. 2011).
NEUROLOGICAL COMPLICATIONS OF ACUTE GASTROENTERITIS WITHOUT DEHYDRATION

Children with gastroenteritis can develop encephalopathy or seizures from causes other than dehydration or electrolyte disturbances. As well as excluding meningitis presenting with vomiting, possible causes to consider include febrile convulsions, heat stroke, hypoglycaemia, acute demyelinating encephalomyelitis, and direct effects from the infecting organisms. The latter includes benign convulsions associated with gastroenteritis, in which children aged 6 months to 3 years with gastroenteritis develop recurrent clusters of focal or secondarily generalised seizures without any associated encephalopathy, typically in the first 3 days of the illness. The interictal EEG is usually normal, but can show focal sharp waves. Magnetic resonance imaging (MRI) is usually normal but can show transient focal lesions. The seizures are often resistant to standard first-line acute treatment, especially with benzodiazepines, but the long-term prognosis is generally good with a low risk of later epilepsy. When associated with rotavirus infection most children do not have cerebrospinal fluid (CSF) pleocytosis or elevated protein level, but polymerase chain reaction (PCR) may detect rotavirus RNA in CSF.

Other direct effects include enteroviral encephalitis and encephalopathy. In one Japanese survey encephalopathy associated with rotavirus infection carried a 12% risk of death and a 25% risk of neurological sequelae, including central motor impairments, intellectual disability and epilepsy. Bacterial enteritides due to organisms such as Salmonella or Shigella species can also present with seizures in younger children, although again dehydration, electrolyte disturbance and hypoglycaemia may all be contributory factors. Rarely, a more severe encephalopathy, known as Ekiri syndrome in Japan, develops in association with cerebral oedema, which can have a poor outcome. The mechanism is unknown. Steroid treatment has been suggested, with little evidence of efficacy (Fig. 27.1).


HEAT STROKE AND HAEMORRHAGIC SHOCK ENCEPHALOPATHY SYNDROME

Although heat stroke often coincides with dehydration, it is due to a direct effect of a raised body temperature on the brain and body, and is the most extreme form of heat-related or heat stress illness. Infants, children and adolescents are at risk in several circumstances: when they are unable to escape from unmonitored enclosed overheated environments such as cots with excess bedding, transport incubators or motor vehicles; when sweating is reduced due to congenital anhydrotic conditions or drugs such as topiramate or MDMA (Ecstasy); or when exercising during hot weather. Immobility, due for example to cerebral palsy (CP), is also a risk factor. In athletes muscle cramps can be an early warning symptom. Presenting features are fever over 40–41°C, nausea and vomiting, dry flushed skin (except in exertional cases when sweating can be profuse), seizures, encephalopathy and multi-organ dysfunction. However, by the time a child reaches medical care cooling may have occurred leaving the other effects as presenting features, which can lead to misdiagnosis as complicated shock due to dehydration or sepsis. MRI shows signal changes in the cerebellum, basal ganglia, hippocampus, and cortex. Treatment relies on immediate cooling to below 40°C and general supportive care. The condition has a significant mortality and morbidity.
The haemorrhagic shock encephalopathy syndrome can be a manifestation of heat stroke in infants and young children, although not all cases appear to be caused by this mechanism. Presenting features are diarrhoea, fever, encephalopathy, seizures, and multi-organ failure including disseminated intravascular coagulation. Neuroimaging shows a range of findings including ischaemia, oedema, and intraventricular and/or parenchymal haemorrhage. The mortality can be as high as 50%, with half of survivors left with neurological sequelae (Bacon 1983; Thébaud et al. 1999; Bytomski and Squire 2003; Jardine 2007; Rogers et al. 2009; Baugnon et al. 2010; Kuki et al. 2015).

HYPERNATRAEMIA

Hypernatraemia, variably defined as a plasma sodium concentration above 145 or 150 mmol/L, most frequently occurs in association with dehydration. In developed countries the highest incidence is in exclusively breastfed infants in the first two weeks of life, due to failure to establish adequate feeding. With treatment, most of this group recover without sequelae. In older infants and children presenting to hospital with hypernatraemia, gastroenteritis is the most frequent cause, predominantly affecting infants under 6 months, and an important minority also have pneumonia. In developed countries most cases now occur after admission during hospitalisation in the context of acute infection, especially in children with pre-existing neurological disorders, such as CP, or following surgery or head injury. The severity of dehydration is more often clinically underestimated, and neurological signs are more prevalent, than in those with non-hypernatraemic dehydration. Clinical signs include drowsiness, jitteriness, hypertonia, hypertreflexia, seizures and coma. Adverse neurological outcomes include epilepsy, stroke, and subdural haematoma. One Tunisian study reported late complications in 6% and death in 11%. Post-mortem findings include cerebral oedema, cerebral venous thrombosis, and intracranial haemorrhage (Hill et al. 1981; Chouchane et al. 2005; Forman et al. 2012; Oddie et al. 2013).

Although for many decades standard management has included the prevention of rapid osmotic shifts by following a slow rehydration regimen and avoiding hypotonic fluids, there is little high level evidence supporting different fluid regimens. Cerebral oedema is still reported, with an associated poor outcome, and may be more frequent in those with higher initial sodium levels and faster rehydration rates. However, most children who develop seizures during rehydration still have a good long-term outcome (Hill et al. 1981; Chouchane et al. 2005; Forman et al. 2012; Oddie et al. 2013).

Other possible causes of hypernatraemia include salt overload, either iatrogenic such as after cardiopulmonary bypass or due to Munchhausen-by-proxy, and endocrine disorders (Table 27.1). These can be distinguished by paired studies of plasma and urine electrolyte urea and creatinine levels (Forman et al. 2012).

Central neurological causes of hypernatraemia are rare. Central diabetes insipidus, reflecting inadequate secretion of antidiuretic hormone, can have acute or chronic presentations, depending on its cause, which also determines the possible associated findings such as visual field defects, disordered thermoregulation, obesity, endocrine and autonomic dysfunc- tion. Causes include a wide range of genetic, malformative and acquired disorders, among which it is always important to consider midline tumours such as craniopharyngioma, and sarcoidosis. Some of these can also cause an often asymptomatic

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<td>Limited water intake</td>
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<td>(often due to inability to access fluid in neurological disorders, or loss of thirst, e.g. post craniopharyngioma resection)</td>
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<tr>
<td>Dehydration due to loss of water through diarrhoea, renal disease or other excessive losses of water with relative electrolyte conservation through hyperpnoea, fever or high ambient temperature</td>
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<td>Salt intoxication (iatrogenic e.g. after cardiopulmonary bypass, or Munchhausen-by-proxy)</td>
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<td>Inappropriate secretion of antidiuretic hormone due to neurological (hypothalamic) disease</td>
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<tr>
<td>Postoperative hyponatraemia</td>
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<tr>
<td>Several neurological diseases (e.g. trauma, tumours, infections, haemorrhage) and non-neurological diseases (e.g. pneumonia)</td>
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<td>Excessive salt loss; gastroenteritis, renal (diabetes insipidus, diuretics, pseudo-hypoaldosteronism, obstructive nephropathy), or through perspiration (cystic fibrosis, heat exhaustion)</td>
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chronic hypernatraemia, with other signs of hypothalamic dysfunction, in the absence of persisting diuresis due to diabetes. ROHHAD (rapid onset obesity, hypothalamic dysfunction, hyperventilation and autonomic dysregulation) syndrome is a presumed autoimmune disorder that can be associated with neuroblastoma, and may account for some cases previously considered to be idiopathic. Cyclophosphamide might improve symptoms in some cases. (Wang et al. 1994; Di Iorgi et al. 2012; Armangue et al. 2012; Jacobson et al. 2016).

HYPONATRAEMIA

Hyponatraemia, variably defined as a plasma sodium level below 130 or 135 mmol/L, can be due to water overload, excess sodium loss, or both (see Table 27.1). Dilutional hyponatraemia most frequently occurs in hospitalised children, with hypotonic infusion fluids a major risk factor. Children at particular risk are those with impaired renal diuresis; for example, due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), treatment with desmopressin, or renal impairment. It is also seen with polydipsia, both psychogenic and in people taking 3,4-methylenedioxymethamphetamine (MDMA, [Ecstasy]). Excess sodium loss is usually associated with dehydration, and can be caused by gastrointestinal or renal losses, cerebral salt wasting syndromes or medication such as diuretics. There can be multiple contributory factors in very sick children receiving intensive care, especially when this is for respiratory illness or follows brain injury of various causes including trauma, neurosurgery, subarachnoid haemorrhage and hypoxaemia (Rogers et al. 2009; Hardesty et al. 2012; Foster et al. 2014; Moritz and Ayus 2014).

When associated with hypertension and proteinuria (the hyponatraemia hypertension syndrome), presenting symptoms can be renal, with polyuria and polydipsia, or neurological: the latter can include headache, vomiting, encephalopathy and papilloedema. Renovascular causes are the most frequent (Kovalski et al. 2012).

Hyponatraemia can occur in children treated with carbamazepine or its derivatives and does not require treatment if asymptomatic.

The main neurological symptoms of hyponatraemia are encephalopathy, with headache, vomiting, ataxia and/or a reduced conscious level, and seizures, which can be focal or generalised. Febrile seizures can co-exist and if so may be more frequent and prolonged. In dilutional hyponatraemia cerebral oedema, hiccups, raised creatine kinase levels and/or rhabdomyolysis have also been reported. Additional neurological features may reflect the underlying pathology; for example, following surgery for brain tumours (George et al. 1996; Hardesty et al. 2012; Lee and Chung 2013; Khow et al. 2014).

Identifying and correcting the underlying fluid balance problem is the most important aspect of treatment, with or without sodium supplementation, if appropriate. A gradual correction of the sodium level is thought to reduce the risk of osmotic demyelination syndrome, but if a child is encephalopathic, hypertonic saline infusion is recommended. Vaptans (vasopressin antagonists) are recommended for non-acute treatment of SIADH (Moritz and Ayus 2014).

OSMOTIC OR CEREBRAL DEMYELINATION

Osmotic or cerebral demyelination syndrome is the umbrella term for both central pontine and extrapontine myelinolysis. Originally recognised at post-mortem, and now mostly by neuroimaging, this can be associated with hyper- and hyponatraemia and hyper- and hypo-glycaemia (Fig. 27.2). Over-rapid correction of hyponatraemia is a classic predisposing factor. Additional factors probably influencing its development include severe liver disease, hypokalaemia and hypophosphataemia. In the central pontine form, a child develops cranial nerve signs, pseudobulbar palsy, quadriplegia and/or ‘locked-in’ syndrome. In the extrapontine form, involving thalamus, basal ganglia, and hippocampus, symptoms are of a more general encephalopathy. The severity varies and does not correlate closely to the imaging appearances. There is no specific treatment. Recovery is usually prolonged, over weeks or months, but the outcome is better in children than adults (Brown and Caruso 1999; Ranger et al. 2012; Moritz and Ayus 2014).

OTHER ELECTROLYTE DISTURBANCES

Some of the possible causes and neurological effects of other electrolyte disturbances are given in Table 27.2. The main
clinical features are neurological in hypocalcaemia, either primary or secondary to hypomagnesaemia, hyperphosphataemia, hypochloraeic alkalosis, and in hypermanganesaemia. Some genetic conditions, usually affecting channel or transport mechanisms, cause neurological disturbances through either direct or associated effects: examples include the hyper- and hypo-kalaemic paralyses (e.g. due to calcium or sodium channelopathies: OMIM 114208, OMIM 603967); hypokalaemic alkalosis and occasionally hypomagnesaemia in Bartter syndrome (OMIM 607364); chloride losing enteropathy (OMIM 214700); the association of dystonia, polycythaeamia and liver disease with hypermanganesaemia due to SLC30A10 mutations (OMIM 613280); and hyper- or hypo-calcaemia due to CASR mutations (OMIM 601199). In hypophosphatasia, pyridoxine responsive seizures can occur due to intracellular pyridoxal phosphate deficiency (Clayton 2006).

Table 27.2 Possible causes and neurological effects of other electrolyte disturbances

<table>
<thead>
<tr>
<th>Electrolyte disorder</th>
<th>Some possible causes</th>
<th>Neurological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcaemia</td>
<td>Vitamin D overdose, hyperparathyroidism, bone destruction, nutritional</td>
<td>Lethargy, myopathy</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>Neonatal; preterm, Vitamin D deficiency; hypoparathyroidism</td>
<td>Jitteriness, tetany, seizures, cramps, paraesthesia</td>
</tr>
<tr>
<td>Hypermagnesaemia</td>
<td>Renal impairment; excess intake</td>
<td>Hyporeflexia, lethargy</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>Renal loss e.g. diuretics; rare genetic form</td>
<td>See hypocalcaemia</td>
</tr>
<tr>
<td>Hypermanganesaemia</td>
<td>Overload; syndromic (SLC30A10)</td>
<td>Dystonia; parkinsonism in adults</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>Phosphate overdose, renal impairment, hypoparathyroidism</td>
<td>See hypocalcaemia</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>Undernutrition, refeeding syndrome, burns, hypophosphatasia</td>
<td>Seizures, encephalopathy; weakness, raised CK, rhabdomyolysis</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Renal impairment; iatrogenic; acidosis; adrenal insufficiency; hyperkalaemic periodic paralys</td>
<td>Weakness; raised CK, rhabdomyolysis</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>GI or renal losses; alkalosis; hypokalaemic periodic paralys</td>
<td>Cramp, fasciculations, weakness, rhabdomyolysis</td>
</tr>
</tbody>
</table>

CK, creatine kinase; GI, gastrointestinal.

**NUTRITIONAL DISORDERS AND THE NERVOUS SYSTEM**

**PROTEIN ENERGY UNDERNUTRITION**

The term malnutrition comprises both protein energy undernutrition and obesity. Childhood protein energy undernutrition is recognised in all parts of the world, with the highest prevalences in Africa and Southeast Asia. Together with associated problems of infection, infestation, micronutrient deficiencies, toxins from foods and other sources, and social deprivation, protein calorie undernutrition is estimated to contribute to 50% or more of global deaths in children aged 5 years or less. It probably has equally significant neurocognitive consequences, although these are less easy to quantify and the relative contributions of undernutrition itself and its associated factors are difficult to distinguish, as discussed below.

Intrauterine growth retardation is an important consequence of maternal malnutrition, when it is often also associated with later child undernutrition. In more affluent parts of the world Intrauterine growth retardation is more commonly caused by placental insufficiency. The incidence varies according to the definition used, but globally it is probably the most frequent type of undernutrition.

As well as an inadequate food supply or famine, other causes of undernutrition include conditions affecting feeding, especially central and peripheral motor disorders, such as some forms of CP and some neuromuscular disorders, or anorexia nervosa; intestinal malabsorption syndromes; cancer, chronic haemodialysis, and chronic liver disease. In more developed countries a significant percentage of hospitalised children are estimated to be undernourished. The highest risk groups include those with chronic neurological problems, although this may be changing with the more widespread use of gastrostomy feeds, and preterm infants or young children especially those receiving intensive care (Cooke et al. 2004; Muller and Krawinkel 2005; Hulst et al. 2006; Pawellek et al. 2008; Grover and Ee 2009; Ahmed et al. 2012; Bhutta and Salam 2012; Duggan 2012; Black et al. 2013; Arthur et al. 2015).

**Clinical Features**

In children and infants with protein energy undernutrition the weight velocity falls first, followed by length and lastly the occipito-frontal circumference. This is reflected by
generalised wasting with loss of body fat and muscle, and is thought to reflect relative preservation of brain growth relative to other body parts, so the child looks thin with a relatively large head. In more chronic forms stunting is more marked. Micronutrient and vitamin deficiencies can add specific signs such as anaemia, rickets or goitre. Classically, the most extreme forms have been divided into marasmus, mainly affecting infants, or kwashiorkor, mainly affecting young children, with the latter distinguished by the presence of oedema, loss of hair colour, skin changes and biochemical disturbances. Kwashiorkor was ascribed to protein deficiency, especially after the cessation of breastfeeding, but it is now recognised that the two overlap and that infestation and infection, especially diarrhoea and HIV, influence the clinical picture (Muller and Krawinkel 2005; Grover and Ee 2009; Duggan 2012).

In neurological terms children are lethargic, miserable and anorexic, with impaired development. Proximal weakness, hyporeflexia, muscle wasting and soft signs may be present in 50% or more, but more classic syndromes such as subacute combined degeneration of the cord are infrequent. Brain MRI shows a reversible diffuse shrinkage without other features. There can be non-specific EEG and evoked potential changes. Nerve conduction studies show slower motor and sensory velocities and reduced sensory amplitudes compared to controls. Nerve biopsies show delayed myelination and segmental demyelination, while muscle biopsies show reduced sarcomere size and grouped fibre atrophy with ultrastructural changes such as myofibril depletion and mitochondrial swelling (Chopra et al. 1986; Agarwal et al. 1989; Chopra and Sharma 1992; Gunston et al. 1992; Odabaş et al. 2005a, 2005b).

**Neurological Complications of the Treatment of Protein Calorie Undernutrition**

Treatment of established protein calorie undernutrition due to starvation involves more than just feeding and can require a staged approach in severely affected children (Grover and Ee 2009). Very early complications such as hypoglycaemia, hypocalcaemia, hyperthermia and infection can cause neurological symptoms on or soon after presentation.

If feeds are re-introduced too rapidly the ‘refeeding syndrome’ can develop, with the hallmark feature of hypophosphataemia, with or without additional electrolyte disturbances (hypokalaemia, hypomagnesaemia, sodium retention with oedema), thiamine deficiency and hyperglycaemia. It typically appears 24–72 hours after feeding is started and if untreated continues for a week or more. Neurological symptoms are due to the electrolyte and other effects and can include encephalopathy, ranging from mild to severe, and peripheral signs, as described in other sections of this chapter. The cardiovascular effects can be fatal. It can follow the introduction of parenteral feeds (the hypophosphatemic-hyperalimentation syndrome). Worldwide this syndrome is probably under-recognised, especially for example, when enteral feeding is introduced in children with CP, or in any child after periods of subacute weight loss or calorie deprivation lasting several weeks.

Management of the electrolyte and glucose disorders and a more graduated calorie intake prevents the syndrome (Fuentebella and Kerner 2009; Crook 2014).

There are also rare reports, mainly in the older literature, of later onset extrapyramidal symptoms with tremors, dystonia and parkinsonian features, developing during the second to fifth week after the reintroduction of feeds. The cause is unknown. The outcome is generally good (Kahn and Falcke 1956; Thame et al. 1994). One adult receiving parenteral feeding showed signal change in the globi pallidi which resolved when manganese was withdrawn (Mirowitz and Westrich 1992).

**Long-Term Neurodevelopmental Effects of Protein Calorie Undernutrition**

Several large studies in different countries have demonstrated adverse effects persisting into adulthood following childhood undernutrition due to starvation, even if the episode is relatively acute. In 40-year-old Barbadian adults who were undernourished in the first year of life, neurocognitive compromise, neuroticism and other specific personality traits were more frequent than in the general population. Smaller studies also associate early malnutrition with reduced head circumference and lower subsequent scholastic achievement. However, there is also an unexplained association between poor head growth due to presumed genetic factors and poor weight gain, that may not be nutritional. The neurocognitive outcome may only partly be due to nutritional factors: associated understimulation may be equally or more important, and interventions incorporating enhanced psychosocial stimulation have considerably more benefit than pure nutritional rescue (Stoch et al. 1982; Ivanovic et al. 2000; Baxter et al. 2009b; Galler et al. 2012; Waber et al. 2014; Grantham-McGregor et al. 2014; Prado and Dewey 2014).

Follow-up studies of neurocognitive outcomes in infants from affluent countries born with intrauterine growth retardation, or small for gestational age, give conflicting results. A Dutch study of adults affected by intrauterine undernutrition during a hunger famine in the Netherlands in 1945 has found smaller head circumferences and attentional deficits in older adults, but in early adulthood no neurocognitive ill-effects could be identified. The effects on the developing brain could be compounded by chronic prenatal hypoxaemia, polycythaemia, the increased risk of birth asphyxia, and by hyperthermia and hypoglycaemia after delivery. It is also a risk factor for CP. However, in this group environmental stimulation and enhancement still have important influences on outcome (de Rooij et al. 2010; Edmonds et al. 2010; Arcangeli et al. 2012; Streimish et al. 2012; Løhaugen et al. 2013; McIntyre et al. 2013; Christensen et al. 2014).

In children with undernutrition due to feeding and swallowing difficulties, gastrostomy feeding is now widely used, with an associated improvement in survival. There is also concern that body weight increases can reflect inappropriate fat
distribution rather than improved muscle mass. The effect on intellectual function is unclear (Vernon-Roberts et al. 2010; Brooks et al. 2014).

Following acute or more prolonged intensive care admissions, preterm infants receiving a greater energy intake than used to be recommended show better general and head growth and an improvement in ultimate brain function and IQ (Lucas et al. 1998; Brandt et al. 2003; Dabydeen et al. 2008).

NON-ORGANIC FAILURE TO THRIVE

Understimulation without undernutrition has also been recognised to be associated with ‘non-organic’ failure to thrive, poor developmental progress, and longer term cognitive, socialisation and motor dysfunctions. Initially recognised in studies of children from orphanges, who either continued in institutional care or were adopted, often internationally, the concept is also applied to children from dysfunctional families. In the latter emotional deprivation is not the only factor, and there is a high risk of continuing growth failure and of physical abuse. Affected children may have behaviour problems, bizarre eating habits, self-mutilation and poor response to pain. The outcome is affected by the duration of the deprivation, and possibly by critical periods as well, so adoption into well resourced and supportive environments may fail to completely reverse the developmental disadvantages. Nonetheless, good post adoption care still has a major positive influence. Iron deficiency may be an independent factor. Non-organic failure to thrive is also used to describe undernutrition due to non-organic feeding disorders, whose features overlap with those above (Skuse 1985; Mouridsen and Nielsen 1990; Garvin et al. 2012; Roeber 2012; Rushton et al. 2013; Doom et al. 2014; Romano et al. 2015).

MICRONUTRIENT DISTURBANCES

Undernutrition is often associated with deficiencies of specific vitamins and trace elements, including minerals, although these micronutrient deficiencies can also occur in isolation (Ahmed et al. 2012). In the latter situation causes can include inadequate dietary intake, transport defects, metabolic errors, inactivation and excess losses.

Iron Deficiency with or without Anaemia

Worldwide, iron deficiency is the most common micronutrient disturbance, affecting both high and low income countries. When associated with anaemia it has well-documented associations with developmental and cognitive under-performance. Pre- and peri-natal iron deficiency is of particular concern as postnatal supplementation may not reverse the effects. However, a causal effect has not been fully proved, partly because of a major confounding effect from socio-economic status and partly due to possible interactions between nutrients. The evidence supporting possible adverse associations with iron deficiency without anaemia is less robust.

Iodine Deficiency

Iodine deficiency is the next most frequent micronutrient deficiency, leading to cretinism, hypothyroidism and/or goitre. According to the World Health Organization, it is the single most important cause of preventable learning difficulties and intellectual disability. Effects can begin prenatally, causing in its most severe form fetal loss, malformations or endemic cretinism. The latter has characteristic neurological findings of severe intellectual disability, hypertonia with mixed pyramidal and extrapyramidal features, hearing impairment particularly affecting higher frequencies, strabismus and, in a minority, basal ganglia calcification. Behaviour problems are strikingly absent. Goitre and growth failure are frequent as well as frank myxoedema. In the last few decades near-universal iodisation of salt has considerably reduced the prevalence (Goslings et al. 1975; DeLong et al. 1985; Halpern et al. 1991; Pharoah and Connolly 1995; WHO et al. 2007; Bhutta et al. 2013; Prado and Dewey 2014). Less severe forms of hypo-iodinism during pregnancy appear to be prevalent in many countries and are strongly suspected to be associated with reduced cognitive function, although this has been hard to prove. In this group, the cognitive effects of iodine supplementation during pregnancy are uncertain and remain under investigation, but are thought to be positive. There is also some evidence that supplementation of mild to moderate deficiency in childhood may improve some cognitive indices (Bath et al. 2013; Pearce 2013; Taylor et al. 2013).

Other Micronutrients

The neurological effects of zinc, selenium and copper deficiencies and of supplementation, both pre- and postnatal, are less clear (Bentley et al. 1997; Picot et al. 2012; Prado and Dewey 2014; Skröder et al. 2015; Warthon-Medina et al. 2015).

VITAMIN DEFICIENCIES

B VITAMIN DEFICIENCIES

Vitamin B1 (Thiamine) Deficiency

Thiamine deficiency was first recognised in people with a restricted diet of polished rice. Routine food supplementation has reduced its prevalence so it now mainly occurs in children as part of the refeeding syndrome when supplementation...
is omitted, when breastfed by a mother with thiamine deficiency, or in association with renal dialysis, neoplasia or gastrointestinal problems including pancreatitis. However, subclinical deficiency may still be widespread in some countries. One outbreak occurred in Israeli infants following the introduction of a thiamine-deficient soy-based formula feed.

In subclinical deficiency, acute symptoms can develop after the administration of a carbohydrate load causing extra metabolic demands, or in association with intercurrent infection. These include signs in varying combinations and severity of high output cardiac failure (‘wet beriberi’); encephalopathy, with lethargy, irritability, and vomiting progressing to a reduced level of consciousness; seizures; hypotonia and brainstem signs such as ptosis, nystagmus, ophthalmoplegia and dysphonia progressing to aphony (a hoarse cry becoming a soundless or reduced cry). Phrenic neuropathy, papilloedema and retinal haemorrhages can be present. Wernicke syndrome, the originally described triad of encephalopathy, oculomotor signs and ataxia, is less common than isolated manifestations or other combinations. Hypoponeraemia and elevated blood and CSF lactate levels can occur. Neuroimaging and pathological findings resemble those found in Leigh syndrome, with symmetrical necrotising lesions affecting the basal ganglia, medial thalamus and brainstem. In thiamine deficiency the mamillary bodies may be involved as well. More chronic manifestations begin with polyneuropathy, which can be painful, with or without ataxia, or in infants with lethargy, vomiting, diarrhoea, cardiomyopathy, dysphonia or aphony and developmental impairment.

Follow up of asymptomatic Israeli infants who received the deficient formula have not shown consistent abnormalities in neurocognitive function. In contrast, symptomatic survivors had a poor long-term outcome with a high risk of epilepsy, including West syndrome, learning difficulties, intellectual disability, pyramidal and extrapyramidal motor dysfunction and persisting brainstem signs. Korsakoff syndrome is well described in adults with thiamine deficiency associated with alcohol abuse, but is very rare in children (Vasconcelos et al. 1999; Coats et al. 2012; Ornery et al. 2013; Mimouni-Bloch et al. 2014).

Vitamin B2 (Riboflavin) Deficiency
Riboflavin deficiency itself does not have recognised neurological associations. One trial of supplementation suggested some improvement in tremor but did not show other convincing improvements in manual dexterity. However, riboflavin supplementation may improve symptoms in Brown-Vialetto-van Laere and related neuropathy syndromes which are caused by mutations in riboflavin transporter genes, as well as in some disorders of fatty acid metabolism (Bates et al. 1994; Bosch et al. 2012; Foley et al. 2014) (see Chapter 9).

Vitamin B3 (Niacin, Nicotinic Acid) Deficiency
Vitamin B3 deficiency mainly causes mouth sores and angular stomatitis. Dietary insufficiency, especially in refugee populations, Hartnup disease, and drugs such as isoniazid are recognised causes. It classically presents as pellagra, a scaly pruritic photosensitive rash, with in addition to gastrointestinal manifestations, ataxia, behavioural abnormalities and, in severe cases, seizures and neurocognitive deficits. In some children, Hartnup disease can present with isolated ataxia or developmental impairment (Malfait et al. 1993; Cheon et al. 2010; OMIM 234500).

Vitamin B6 (Pyridoxine, Pyridoxal, Pyridoxamine) Deficiency
Pyridoxine deficiency is very rare. The largest outbreak was in the early 1950s when a milk formula feed was introduced in the United States with a low pyridoxine content. Only a small proportion of infants developed symptoms, usually between 2 and 4 months of age. These were initial hyperirritability and apparent gastrointestinal colic, with regurgitation, followed by tonic posturing and focal or generalised seizures, which could be precipitated by sound, movement and feeding and which were responsive to phenobarbital or protein restriction. Follow-up showed no persisting clinical or EEG abnormality (Coursin 1955; Bessey et al. 1957).

In adults, deficiency is associated with skin and mucous membrane changes (eczema, cheilosis, angular stomatitis, glossitis), anaemia and seizures. Similar symptoms can be induced by inactivation of pyridoxal phosphate by agents such as isoniazid, and Ginko fruit. Pyridoxine is also used prophylactically to prevent isoniazid induced neuropathy and to treat seizures in acute isoniazid poisoning (Shah et al. 1995).

Pyridoxine dependency (antiquitin deficiency, ALDH7A1 deficiency) and pyridoxal phosphate-dependent conditions are covered in Chapter 9.

Vitamin B9 (Folic Acid, Folinic Acid) Deficiency
The main features of folate deficiency are non-neurological: megaloblastic anaemia, mouth ulcers, and a sore, red tongue. Mood change is often reported but intervention studies in adults have not shown definite benefits from supplementation. The main neurological risk in adults is through the secondary effects of an elevated homocysteine level with an associated thrombotic tendency.

Acquired deficiency occurs through dietary insufficiency or malabsorptive states, especially coeliac disease and small bowel bacterial overgrowth. Some anticonvulsant medications are also associated with deficiencies, although other factors may be involved as well. Infants with the rare condition congenital folate malabsorption, due to mutations in the SLC46A1 transporter, present with anaemia and failure to thrive. If untreated, developmental impairment, seizures (some occipital), ataxia or athetosis can develop, together with cerebral calcification (OMIM 229050).

Cerebral folate deficiency is diagnosed when CSF 5-methyltetrahydrofolate levels are low despite normal blood
folic acid. In addition, in some infants with multiple anomalies, folate deficiency can be associated with a microcephaly without normal folate levels. Most children present in the first 2 years of life with sleep disturbance followed by regression, ataxia, cerebellar atrophy, leuko-encephalopathy, microcephaly and, later in childhood, hearing impairment and polyneuropathy. One very rare cause is a defect in the FOLR1 folate receptor gene which presents in early infancy with the above features as well as seizures. An acquired deficiency due to antibodies against the folate receptor is also proposed. More controversially, cerebrofolate deficiency is also reported in some children with conditions such as Rett syndrome and mitochondrial cytopathies. It is recommended that affected children should be treated with folic acid rather than folate (Hyland et al. 2010; Grapp et al. 2012; OMIM 613068).

The importance of peri-conceptual folate supplements in reducing the risk of neural tube defects is well established. More controversial is a suggested link to the prevention of autism.

**Vitamin B12 (Cobalamins) Deficiency**

Deficiency of vitamin B12 can complicate a strict vegan diet, malabsorption syndromes, surgical removal of the terminal ileum, pernicious anemia, fish tapeworm infestation, and some inborn errors of cobalamin transport or metabolism. It is also recognised in some adults with AIDS. Inactivation by agents such as nitrous oxide anaesthesia can precipitate symptoms in people at risk. In children and adults the main neurological presenting features are those of a sensory neuropathy and/or a myelopathy affecting the doral and lateral columns, the classic syndrome of subacute combined degeneration of the cord. Depending on the predominant pathology these comprise paraesthesia, sensory ataxia and extensor plantar responses, while deep tendon reflexes can be exaggerated or reduced. Friedreich ataxia and vitamin E deficiency can cause similar findings. Optic atrophy also occurs. MRI shows increased signal in the posterior cord on T2-weighted imaging, which does not enhance, associated with cord swelling. Some patients also have focal areas of cerebral white matter signal change. Most cases will be associated with a megaloblastic anaemia, as well as raised plasma homocysteine levels and methylmalonic aciduria. In adults, wider effects can include cognitive and psychiatric features. Prompt treatment resolves the symptoms. As treatment with folic acid can exacerbate symptoms, it is important to fully investigate megaloblastic anaemia before starting any treatment (Healton et al. 1991; Facchini et al. 2001; Rasmussen et al. 2001).

Congenital B12 deficiency occurs in breastfed infants born to B12 deficient mothers, who may themselves be asymptomatic. Failure to thrive is the earliest feature, starting in the first 6 months of life, followed by non-specific features of apathy, hypotonia, developmental impairment, anorexia and vomiting, that in severe cases can progress to seizures, regression and microcephaly. Most have anaemia, but it is not always megaloblastic. Brain imaging can be normal or show global atrophy and delayed myelination. While treatment leads to an immediate improvement, a self-limiting movement disorder, comprising focal or generalised tremor and myoclonus especially affecting the face, can occur or worsen with treatment. It responds to clonazepam. Some children have also developed West syndrome either as a presenting feature or some weeks after treatment started. Many affected infants have a poor prognosis with persisting intellectual deficits (Ozer et al. 2001; Rasmussen et al. 2001; Dror and Allen 2008; Honzik et al. 2010; Malbora et al. 2014).

**LIPOSOLUBLE VITAMIN DEFICIENCIES**

**Vitamin D (Colecalciferol, Ergocalciferol)**

Vitamin D is not really a vitamin but a hormone precursor. Deficiency is probably much more prevalent globally than previously suspected, affecting, for example, approximately one-third of French children in one survey. However, as the definitions of normal levels have not been agreed internationally, the exact prevalence is still uncertain. At risk groups include those with dietary deficiency, malabsorption, and reduced exposure to sunlight due to climate, clothing or skin pigmentation, singly or in combination. Treatment with some drugs, including anticonvulsants such as phenytoin and phenobarbital, has been associated with deficiency, especially in institutionalised children, but additional factors may play a part. Calcium deficiency is now recognised to be an important contributory factor as well.

Rickets, the most obvious manifestation, can be one cause of a large anterior fontanelle with delayed closure (others include hydrocephalus, hypothyroidism, hypoparathyroidism or cranioceleidodyostosis). Other neurological features include hypocalcaemic seizures, weakness, and pain both of bone and muscle origin. While overt childhood rickets, or osteomalacia in adolescents, is still rare in developed countries, more subtle manifestations of deficiency such as proximal muscle weakness and musculoskeletal pain without obvious bony changes appear more widespread, especially in younger children. Some more severe cases can present as possible myopathies, with loss of ambulation due to weakness.

Maternal vitamin D deficiency in pregnancy can cause symptomatic hypocalcaemia in neonates. The optimal intake of vitamin D during pregnancy is unknown.

A possible role of vitamin D in acute or chronic demyelinating conditions such as multiple sclerosis, and in clinical depression, is currently being investigated, without definitive results yet available (Cimaz et al. 2000; Al-Said et al. 2009; Munns et al. 2012; Vidalhiet et al. 2012; Prentice 2013; Thacher et al. 2013; Torun et al. 2013; Elder and Bishop 2014).

**Vitamin E (Tocopherols and Tocotrienols)**

The neurological manifestations of a deficiency of alphatocopherol, the active form of vitamin E in humans, resemble those seen in Friedreich ataxia, with a sensory neuropathy and spino-cerebellar degeneration. Additional features can include head titubation, dystonia, pigmentary retinopathy, cardiomyopathy and cerebellar atrophy on imaging. Dietary deficiency has never been reported, so children are only affected
if they have a genetic defect in vitamin E transport (ataxia with vitamin E deficiency), or fat malabsorptive states, such as for example abetalipoproteinemia, or cystic fibrosis especially when complicated by liver disease. Early supplementation prevents neurological problems but delayed therapy may not fully reverse them. Newborn infants, especially born preterm, can also have low levels. The role of routine supplementation in the prevention of intraventricular haemorrhage or retinopathy of the newborn remains controversial. Excess vitamin E can cause a myalgic myopathy with raised creatine kinase (Kohlschütter 1993; Cavalier et al. 1998; OMIM 277460).

**Vitamin K (Phylloquinone, Menadionones)**

As vitamin K deficiency causes a coagulopathy, intracranial haemorrhage can occur, often with severe neurological consequences. At risk groups include breastfed neonates and children with malabsorption or liver disease. Routine administration at birth has largely prevented early (first week) vitamin K deficiency haemorrhage, previously called haemorrhagic disease of the newborn, but a later onset form is still reported in many countries. Parts of Southeast Asia have a particularly high prevalence. Many affected infants have additional problems, especially liver and biliary disorders. The most effective prophylaxis is still being assessed. In theory, infants of mother taking enzyme-inducing drugs such as some anticonvulsants could be at risk of deficiency, but there is insufficient evidence to recommend routine supplementation. Excess vitamin K3 (menadione) can contribute to bilirubin encephalopathy (Puckett and Offringa 2000; Harden et al. 2009; Busfield et al. 2013; Elalfy et al. 2014).

**Other Deficiencies**

The possible importance of long-chain polyunsaturated fatty acids in the developing brain, and routine supplementation of bottle milk, has been under investigation since studies suggesting that children who had been breastfed showed a superior performance to those who had been bottle fed. Early studies suggested improved visual and developmental performance after supplementation in young children, but more recent studies have had conflicting results (Fleith and Clandinin 2005; Leung et al. 2011; Willatts et al. 2013).

**TROPICAL PARAPLEGIAS, TROPICAL ATAXIC NEUROPATHY AND NUTRITIONAL OPTIC NEUROPATHY**

A group of conditions with overlapping features of neuropathy, myelopathy, optic neuropathy or sensorineural deafness have been reported in association with undernutrition, which may be due to ingested toxins, although the exact cause is often uncertain. Deficiencies of vitamins B1, B3, B9, B12 and E all enter the differential diagnosis.

They are divided into two main groups. In the first, tropical paraplegia, signs of spastic paraplegia predominate, sometimes of acute onset, without sensory features. Currently recognised causes include lathyrism, konzo and human T lymphotropic virus type-1 (HTLV-1) infection. Lathyrism is now localised to Bangladesh, India and Ethiopia, and is due to ingestion of grass pea seeds cooked in clay pots. Konzo has similar clinical features, with added neurocognitive impairments, and occurs in localised epidemics, mainly in Africa, due to incorrect processed cassava. Children infected by the retrovirus HTLV1, probably by vertical transmission from their mothers, can develop early signs of myelopathy. The manifestations in adults are wider and include cognitive effects, cerebellar disorders and facial and peripheral neuropathies as well as myelopathy (Getahun et al. 2005; Kendall et al. 2009; Souza et al. 2012; Boivin et al. 2013).

The second group, tropical ataxic neuropathy, was originally recognised in adults, where a painful neuropathy with associated sensory ataxia developed in some with undernutrition. Although now less prevalent, it is still reported in countries such as Nigeria. Some cases may be related to thiamine deficiency (Ogunlesi 2004).

Nutritional optic neuropathy presents with visual impairment due to a central scotoma, associated with disc pallor. An outbreak in Cuba in the early 1990s was linked to nutritional factors, although it responded in part to vitamin supplementation (Hedges et al. 1997). Toxic forms linked to smoking may be due to an underlying Leber’s Hereditary Optic Neuropathy.

Nodding syndrome affects school age children in parts of Tanzania, Uganda and Sudan. In it the pathognomonic head nodding is associated with progressive neurodegeneration, epilepsy and growth failure. The cause is unknown, although there is an epidemiological association with onchocerciasis (river blindness), as well as poverty and undernutrition. An autoimmune aetiology has been postulated (Idro et al 2016).

**OTHER INGESTED TOXINS: HEAVY METALS**

Lead neurotoxicity is covered in Chapter 13. Severe methylmercury poisoning of the fetus leads to Minamata disease, comprising microcephaly, severe intellectual disability, and CP. Lower level exposure occurs in pregnant women with a high dietary fish intake, and may have adverse cognitive effects (Myers and Davidson 1998; Axelrad et al. 2007). There is some evidence that low level exposure to other heavy metals may also affect cognition and behaviour (Sanders et al. 2015). High level exposure to such toxins is often occupational so children are at lower risk, but mercury toxicity is associated with ‘Pink disease, which includes a painful peripheral neuropathy, and manganese toxicity can cause parkinsonism and basal ganglia signal changes.

**OBESITY**

Primary obesity is receiving increasing priority as a public health problem in some countries. Specific neurological complications in childhood include those related to the metabolic syndrome (arterial hypertension, raised blood glucose and
dyslipidaemia) and to sleep apnoea, chronic daily headache, and idiopathic intracranial hypertension, especially in adolescent girls. In adults there is an increased risk of chronic pain, stroke, and compression neuropathies such as carpal tunnel syndrome (Robberstad et al. 2010; Brara et al. 2012; Pakalnis and Kring 2012; Andrews et al. 2014).

Secondary obesity is associated with neurological problems through the underlying aetiology, and can be either genetic, as for example in Prader-Willi syndrome, or acquired, as in endocrine disorders, or in autoimmune conditions such as ROHHAD and narcolepsy-cataplexy. Excess weight gain can also be an adverse effect of some anticonvulsant or neuroleptic drugs.

**DIABETES**

**Acute and Chronic Encephalopathies in Children with Diabetes Mellitus**

Diabetic ketoacidosis and the rarer hyperosmolar hyperglycaemic state without ketoacidosis both have major risks of neurological complications. Ketoacidosis is more frequent in newly diagnosed than established cases, but has become less frequent in both. Ketoacidosis as an initial presentation varies six-fold between different countries, for several possible reasons. While ketoacidosis presents with features of dehydration, the level of consciousness correlates best with the degree of acidosis. Neuroimaging suggests that subclinical oedema is present in over 50% of cases, but in approximately 1% of episodes during treatment severe symptomatic cerebral oedema can develop, for reasons that are still unclear. The main symptom is a deterioration in conscious level, often several hours after an initial recovery from the ketoacidosis, but in those with a reduced conscious level at presentation a failure to improve should also suggest the possibility. Additional features can include hypertension, bradycardia, pupillary changes and decorticate or decerebrate posturing. Clinical signs such as papilloedema and signs of oedema on neuroimaging are not always reliable diagnostic criteria, especially in the early stages. Despite fluid management and intensive therapy this complication has a high risk of death and, in approximately one-third of survivors, of severe motor and cognitive sequelae. Stroke and osmotic demyelination syndrome have also been described as rarer complications of ketoacidosis (Edge et al. 2001; Edge et al. 2006; Glaser et al. 2006; Petzold et al. 2011; Usher-Smith et al. 2012).

The hyperosmolar hyperglycaemic syndrome, without keto-acidosis, is rare in childhood, although is becoming more frequent with the increasing prevalence of type 2 diabetes associated with obesity where it can be the first presentation. However, most episodes still occur in children with type 1 diabetes. Initial symptoms are those of dehydration, such as lethargy, confusion and dizziness. If untreated some then develop a reduced conscious level, at times associated with seizures, hemiparesis and/or ophthalmoplegia. Stroke and rhabdomyolysis may occur, as well as renal failure, hyperthermia and pancreatitis, but cerebral oedema is unusual (Zeitler et al. 2011; Bagdure et al. 2013).

In a child with established diabetes, the other major cause of a reduced level of consciousness is hypoglycaemia. Acutely, it presents with autonomic features of a stress response, such as pallor, sweating, hunger and anxiety, which can be reduced if a child is taking beta-blocking drugs or in deep sleep. Neurological symptoms include drowsiness, headache, dizziness, blurred vision and slowed neurocognitive performance which progress to seizures and coma if untreated. Some children also develop focal seizures and/or hemiparesis. Early symptoms are often unrecognised by adolescents with mild hypoglycaemia. This age group is also at particular risk of nocturnal hypoglycaemia, especially after exercise (Ryan et al. 2006; Tamborlane et al. 2007).

Most children develop diabetes mellitus through an autoimmune mechanism, which is associated with an increased risk of other autoimmune disorders including autoimmune encephalopathies, although this appears to be uncommon.

While long-term neurological impairments can follow these acute events, children with diabetes appear to be at risk of usually small reductions in a range of neurocognitive functions including IQ, motor speed, attention, reading and visuospatial abilities. Some causes of diabetes mellitus have neurological associations, such as mitochondrial disorders or specific syndromes such as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness or Rogers [thiamine responsive megaloblastic anaemia, diabetes and deafness] syndrome. Neonatal diabetes has a range of genetic causes, some of which also cause developmental impairment, epilepsy and muscle weakness. Mutations in potassium channel subunit genes form the largest subgroup, in whom early high-dose sulphonylurea therapy is associated with an improved neurodevelopmental outcome. Otherwise onset before 6 years of age, severe hypoglycaemia and chronic hyperglycaemia are suspected contributory factors, although their relative importance and exact relationships with specific functions are less consistent across different studies. Early onset may be linked to attentional and learning difficulties and severe hypoglycaemic episodes to poorer short-term verbal memory. Short periods of hypoglycaemia do not appear to cause neurological harm. In a wider context, the long-term neurocognitive effects of hypoglycaemia from all causes are strongly affected by aetiology, comorbidities and whether acute status epilepticus occurred, but less so by age and glucose level. Neuroimaging findings in adults with diabetes are affected by vascular and other complications. In children there may be reductions of grey matter volume in specific regions such as the cerebellum and occipital cortex, which are of uncertain significance. In adults
with diabetes severe hypoglycaemia is not clearly associated with damage on neuroimaging (Ryan et al. 2006; Gaudieri et al. 2008; Perantie et al. 2008; Naguib et al. 2009; Lin et al. 2010; Gataullina et al. 2012; Hannonen et al. 2012; De Franco et al. 2015; OMIM 222300; 249270 and 600937).

**Acute Hemiplegia**

When acute hemiplegia occurs during hypoglycaemia it responds promptly to glucose infusion.

Transient acute hemiparesis on waking is also a classic indicator of nocturnal hypoglycaemia in children with diabetes mellitus, and more recently it has also been recognised as a manifestation of low cerebroglucose levels due to Glut1 deficiency. However, in children with diabetes it can also occur in the absence of documented hypoglycaemia. In some but not all, a brief seizure can occur, but this does not appear to be a form of Todd paresis. In this situation a glucose infusion is less effective, but the prognosis is still good with spontaneous resolution after a few hours. Recurrences may occur and be ipsi- or contra-lateral. Persistent hemiparesis can rarely occur. The mechanism is unclear, as there is little to support suggestions of hemiplegic migraine or transient ischaemic attacks. Neuroimaging, which is usually indicated to exclude other possible causes, is normal, while EEG shows contralateral or generalised slowing. In adults, diabetes mellitus is a risk factor for stroke in but this is not reported in children except in association with hyperglycaemic episodes (Poccecco and Ronfani 1998; Shehadeh et al. 1998; Fernández-Mayoralas et al. 2004).

**Peripheral, Focal and Autonomic Neuropathy**

The well-recognised adult complication of diabetic peripheral polyneuropathy, often painful, is clinically unusual in children. However, even after a few years approximately a third of children and adolescents with diabetes show subclinical evidence of large and small fibre polyneuropathy. There is a correlation with other microvascular complications and with glycaemic control. Cranial and other mononeuropathies are also rare in children with diabetes, although cases have been reported and again subclinical involvement can be detected by specific testing. The same applies to autonomic neuropathy where subclinical features are associated with glycaemic control, duration of the condition and some genetic factors, but not with polyneuropathy. Visual impairment due to retinopathy is a late complication. Optic neuropathy of vascular origin may also occur (Aicardi et al. 2009; Blankenburg et al. 2012; Höllner et al. 2013; Tang et al. 2013).

**Neurological Consequences of Hypoglycaemia**

Outwith hypoglycaemia complicating diabetes mellitus, severe prolonged hypoglycaemia of any origin, especially in neonates and/or if symptomatic, has significant long-term cognitive and other effects, which are age related. Neonates can tolerate lower glucose levels than older children without showing symptoms such as seizures. While such ‘asymptomatic’ neonatal hypoglycaemia was thought to have a good prognosis, even this is now recognised to lead to similar adverse outcomes. Blood levels below 1mmol/L for more than 1–2 hours are considered particularly likely to cause harm. Persistent or recurrent hypoglycaemia due to various genetic syndromes causing congenital hyperinsulinaemia (previously called nesidioblastosis) is associated with adverse neurocognitive outcomes both through direct genetic mechanisms and secondary to hypoglycaemia. These include cortical visual impairment, learning difficulties, microcephaly and occipital epilepsy, but absent or mild motor signs except in very severe cases. Seizures are generally infrequent and responsive to treatment, with a low risk of status epilepticus.

MRI studies show a range of abnormalities including white matter swelling and damage, especially in the parieto-occipital region, which can be cystic; encephalomalacia and global atrophy can occur, which may be unilateral; haemorrhage and stroke; and basal ganglia changes especially in the globus pallidus and thalamus. Neonates typically develop often asymmetrical posterior parieto-occipital white matter signal change. In some, early changes may resolve on follow up, but in others later localised atrophy indicates permanent damage. In older children with hypoglycaemia associated with inborn errors of metabolism occurring between 6 and 22 months the basal ganglia are more often affected and after that age the parieto-temporal cortex (Kinnala et al. 1999; Christiaens et al. 2003; Caraballo et al. 2004; Ryan et al. 2006; Boardman et al. 2013; Gataullina et al. 2013; Marzelli et al. 2014; OMIM 256450) (Fig. 27.3).

**THYROID DISEASES**

Thyroid hormones are crucial to normal neural maturation and function. In the human fetus, thyroxine (T4) is synthesised after 10–14 weeks gestation, so before then fetal thyroid hormones derive solely from the mother, although the maternal contribution remains important throughout pregnancy. In animal studies, thyroid hormones are vital for all aspects of mid and late gestational neurological development, such as neuronal proliferation, migration, synapse formation and myelination, both in the cortex and cerebellum (Williams 2008). The effects of early hypothyroidism due to iodine deficiency are described in the Iodine Deficiency section above.

**Congenital Hypothyroidism**

Without areas of iodine deficiency, congenital hypothyroidism can be caused by a variety of structural or metabolic causes, with an incidence of approximately one in 3000–4000 births, more frequently in girls than boys. As at least half the infants are asymptomatic and as early treatment affects the
neurodevelopmental outcome, many countries now have national neonatal screening programmes. Depending on what is screened, a few children may still be missed: for example, if thyroid stimulating hormone (TSH) levels are used, cases of central origin will not be detected. Untreated infants can have hypotonia, sleepiness, macrogllossia, a grunting cry, umbilical hernia, sparse hair, a wide fontanelle and separated sutures. Prolonged neonatal jaundice is an important clue. If untreated, in addition to developmental impairment, ataxia or less frequently spasticity can develop in up to one-third of children and sensineural hearing impairment in 20%.

If detected by screening and treated appropriately within two weeks, the outcome is normal in most children. However, in those with severe deficiency, even early treatment does not fully reverse the effects as follow up at 10 years shows a persisting 10 point IQ difference from those with milder deficiency and control groups. Mild deficits in visuospatial and memory functions can also occur. In view of this, high-dose early treatment has been tried but with uncertain benefits and with risks of behaviour difficulties and premature suture fusion. In those treated later, up to 2 months of age, IQ is reduced and there is a risk of motor dyspraxia and hearing problems (Smith et al. 1975; Vanderschueren-Lodewyckx et al. 1983; Simons et al. 1994; AAP et al. 2006; Mann 2011; Bongers-Schocking et al. 2013).

Some epidemiological data suggests that maternal hypothyroxaemia during pregnancy may be associated with cognitive difficulties in children. However, replacement therapy seems to have little benefit. Maternal thyroid dysfunction is also an important risk factor for neonatal encephalopathy and CP (Badawi et al. 1998; Henrichs et al. 2010; Lazarus et al. 2012; Ghassabian et al. 2014).

Thyroid dysfunction can also be associated with learning disabilities through a common aetiology. Down syndrome is associated with an increased risk of both congenital and acquired thyroid disorders. Impaired function of the NKX2-1 (previously TTF1) gene causes ‘benign hereditary chorea’ and other movement disorders, congenital thyroid dysfunction and lung disorders. Children present with hypotonia, motor delay and chorea which improves during childhood, while myoclonus becomes more prominent. Upper limb dystonia and tics can occur. Learning difficulties are frequent. Abnormal thyroid hormone transport in the X-linked disorder SLC16A2 (previously MCT8) causes Allan-Herndon-Dudley syndrome in affected boys: severe non-progressive intellectual disability with severe speech impairment, early onset nystagmus, paroxysmal movement disorders often precipitated by nursing manoeuvres and stopped by neck flexion, ataxia, progressive hypertonia and contractures, later epilepsy, and muscular atrophy and weakness with very poor head control. Features of hypothyroidism with normal or raised thyroid hormone levels can be due to mutations in thyroid receptor genes such as TR-alpha (Schwartz and Stevenson 2007; Gras et al. 2012; King et al. 2014; Peall et al. 2014; OMIM 610978; 300523; 190120).

Childhood Onset Hypothyroidism

In contrast to congenital forms, the neurological associations of acquired childhood hypothyroidism have been little studied. It is associated with cognitive problems affecting attention and school performance. After treatment is started behaviour problems, headache and concentration difficulties can occur, together with, if anything, slight decreases in some cognitive tests. Rarely, papilloedema and idiopathic intracranial hypertension can occur which respond to a reduced dosage. However, the effect of milder subclinical hypothyroidism is more controversial with some studies in adolescents suggesting higher scores on certain cognitive tests than euthyroid peers. This has obvious implications for treatment if investigations reveal mild biochemical hypothyroidism. Children with Down syndrome are at particular risk of both overt and subclinical hypothyroidism, so screening is recommended, but the optimal therapy is still debated (Rovet et al. 1993; Prasher 1999; Wu et al. 2006; King et al. 2014).

Hypothyroidism is also recognised as a rare cause of entrapment neuropathy, particularly carpal tunnel syndrome, in children. The Kocher-Debre-Semelaigne syndrome is the association of limb muscle hypertrophy, with slow contraction and relaxation, and raised creatine kinase levels in children with untreated, often congenital, hypothyroidism. Myopathy with elevated creatine kinase levels and occasionally acute rhabdomyolysis is well recognised although rare. In adults a range of other myopathies have been associated (Tullu et al. 2003; Gunther et al. 2006; Monzani et al. 2012; Potulska-Chromik et al. 2014).

Hashimoto Encephalopathy

Hashimoto thyroiditis is an autoimmune disorder of the thyroid, while the term Hashimoto encephalopathy (or syndrome)
has been used to describe neurological problems associated with raised antithyroid peroxidase or thyroglobulin autoantibody levels (see also Chapter 12). The condition is presumed to be of autoimmune origin, especially as symptoms often respond to steroid treatment, but due to uncertainty over the precise pathogenesis, it is now suggested that it should be termed ‘steroid responsive encephalopathy associated with autoimmune thyroiditis’ (SREAT). As not all cases respond to steroids, the term ‘encephalopathy associated with autoimmune thyroid disease’ has been proposed as more accurate. Since thyroid auto-antibodies are relatively prevalent in the general population some cases may be coincidental. Despite the association, approximately half of patients have normal thyroid function. Symptoms are very varied, acute or subacute, and can fluctuate. Singly, or in combination, they include psychological features, especially behavioural change, hallucinations and sleep problems; acute encephalopathy; seizures including status; focal motor deficits; ataxia; movement disorders, and deterioration in school performance. It used to be believed to only affect older children and adolescents but much younger onsets are now being recognised, at the age of 3 years or less. EEGs are often but not always abnormal, usually with non-specific findings such as slow activity but in some with epileptiform changes. MRI is often normal but can show hippocampal hyperintensity on T2 imaging, or non-specific white matter signal change. Symptoms respond to steroids and other immunomodulatory agents, with a relatively good prognosis if treated early (Armangue et al. 2012; Mamoudjy et al. 2013; Olmez et al. 2013).

Hyperthyroidism

Hyperthyroidism, often of autoimmune origin, can also be associated with Hashimoto encephalopathy. ‘Thyroid storm’, comprising altered level of consciousness, tachycardia, hypertension, fever and other symptoms, is a very rare medical emergency in children. More usually, hyperthyroidism enters the differential diagnosis of tremor and can present with cognitive or psychological symptoms such as falling school performance, emotional lability, hyperactivity or dyssomnias. More florid psychiatric features and seizures are rare complications in adults but are not reported in children. Moyamoya has also been associated in adults and more recently in children too. Exophthalmos can be associated with oculomotor myopathy. In adults hyperthyroidism can also cause myopathy, periodic paralysis and myasthenia gravis, but these are not reported in children (Aslan et al. 2011; Li et al. 2011).

OTHER ENDOCRINE DISORDERS

The neurological symptoms of parathyroid disease are directly related to calcium and phosphorus metabolism, as has been described elsewhere (Chapters 2 and 10). They include CNS manifestations and may present as neuromuscular syndromes, psychiatric disease in adults, and compression of neural structures by bone abnormalities (Tonner and Schelte 1993).

Pituitary disorders have been considered in Chapter 14. While most are acquired, the congenital neonatal form is often genetic in origin with mutations identified in at least ten genes that are involved in pituitary development. Diagnosis can be difficult but indicators include prolonged hypoglycaemia, prolonged jaundice, either unconjugated or conjugated, and microphthalmus which is more easily detected in boys. Birth weight is usually normal. Depending on the cause, associated features can include midline defects involving the face and/or brain, such as septo-optic dysplasia and holoprosencephaly. Others can have the triad of ectopic posterior pituitary, pituitary aplasia or hypoplasia, and stalk defects. Those with structural problems are more likely to have multiple hormone deficiencies as opposed to isolated growth hormone deficiency. If a child with the neonatal form of hypopituitarism is treated promptly with growth hormone the outcome is usually normal but if not neurocognitive problems can follow (Alatzoglou and Dattani 2009; Castinetti et al. 2012; Deal et al. 2013).

Congenital idiopathic hypogonatrophic hypogonadism presents later and has a wide range of possible genetic causes. Additional features can include anosmia (Kallmann syndrome), sensorineural hearing impairment and learning difficulties (OMIM 147950).

Acute lymphocytic hypophysitis is a rare acute condition mainly described in adults, particularly women of childbearing age, but a few cases can occur in children and adolescents. It is thought to be of autoimmune origin. The presenting features include headache, nausea and vomiting which can be cyclical, fatigue, dizziness and symptoms of endocrine insufficiency, such as diabetes insipidus or hypocortisolism. There may be a CSF pleocytosis. MRI studies show enlargement of the gland and stalk often with contrast enhancement. If this is marked, compressive symptoms such as visual field defects can occur. The differential includes other causes of pituitary enlargement and dysfunction such as tumours, infections and inflammatory or granulomatous conditions, so definitive diagnosis requires a biopsy. High-dose corticosteroid therapy is the initial treatment, but debulking may be required. Long-term endocrine replacement therapy may also be necessary (Kalra et al. 2011; Allix and Rohmer 2014).

Adrenal Insufficiency (Addison Disease)

In younger boys particularly, adenoleukodystrophy usually presents with adrenal insufficiency some years before the onset of neurologic symptoms. Some may never develop the leukodystrophy, but require long-term follow up due to the risk of adrenomyeloneuropathy later in life. Otherwise tubercular, autoimmune and mitochondrial causes of adrenal insufficiency can also be associated with neurological involvement (Korenke et al. 1997).

Adrenal insufficiency itself causes weakness, fatigue, cramp and myalgia, in association with disturbances in electrolytes and occasionally hypoglycaemia, which rapidly respond to steroid
replacement. Idiopathic intracranial hypertension can be the presenting feature (Condulis et al. 1997).

Genetic associations include a contiguous gene deletion on the X chromosome which can cause simultaneous congenital adrenal hypoplasia, Duchenne muscular dystrophy and glycero kinase deficiency, and Addison, alacrimia, and achalasia (AAA) syndrome, which can also be associated with spasticity, optic atrophy or peripheral neuropathy (OMIM 300679 and 231550).

Steroid Myopathy
Steroid myopathy is a well-characterised complication of both acute and chronic corticosteroid therapy, or Cushing disease, associating proximal weakness, wasting and myalgia with type 2 fibre atrophy on muscle biopsy. In children, most reported cases are in children receiving treatment for juvenile chronic arthritis in which case dermatomyositis enters the differential diagnosis (Naim and Reed 2006).

Cardiac Disorders

Neurological Complications of Non-Operated Congenital Heart Disease

Cognitive and Motor Development and Heart Malformations

Most children with congenital heart disease have normal neurocognitive function. However, congenital heart defects are nonetheless associated with an increased risk of neurodevelopmental impairment, through mechanisms such as shared genetic aetiologies, a higher chance of structural brain abnormalities, and probable effects on brain growth and development beginning in utero. The neurological risk also correlates to the complexity of the underlying cardiac defect, being lower in forms such as uncomplicated ventricular septal defect and higher in conditions such as transposition of the great arteries or hypoplastic left heart syndrome. Postnatally chronic hypoxaemia and other complications of cyanotic heart disease and postoperative neurological complications also contribute. With improved survival especially in more complex conditions, earlier intervention, and changes in bypass techniques the outcome has been changing in more recent series (Wright and Nolan 1994; Stieh et al. 1999; Limperopoulos et al. 2010; Marino et al. 2012; Ortinau et al. 2012; Ortinau et al. 2013; Brossard-Racine et al. 2014).

Down syndrome and 22q deletion are the first and second most common recognised causes of congenital heart disease, and both have significant neurological and intellectual associations. Other recognised conditions associating cardiac and neurodevelopmental problems include Aarskog-Scott, Alagille, Noonan, PHACE (posterior fossa brain malformations, hemangiomas of the face, arterial anomalies, cardiac anomalies, and eye abnormalities), Turner, and Williams syndromes. Conversely coarctation of the aorta may be associated with cerebral aneurysms and may also produce cerebral haemorrhage in their absence (Freedom 1989; Marino et al. 2012).

In clinical terms children with more complex disease have a higher risk of microcephaly and of abnormal neurological behaviour in infancy. Outcome studies in children and adults with complex congenital heart disease show an increased risk of developmental disability involving motor skills, intelligence, school and employment achievement, and attentional, speech, language and social abilities.

Fetal and neonatal neuroimaging studies have shown structural abnormalities in 18–40% of fetuses with congenital heart disease including ventriculomegaly, which was the most frequent, agenesis of the corpus callosum and vermal hypoplasia. In addition there is an important prevalence of white matter abnormality, intraventricular haemorrhage and microstrokes prior to any intervention, confirmed by pathological studies, again particularly in those with more complex forms of congenital heart disease. Finally, there appears to be a specific failure of brain growth in the third trimester, especially with conditions that restrict output from the left ventricle, as well as delayed maturation and altered circulation indices. How these all correlate with cognitive outcome is still mainly to be defined, although brain volume has been shown to correlate to cognitive function in adolescents with congenital heart disease (Limperopoulos et al. 1999; Miller et al. 2007; Block et al. 2010; Limperopoulos et al. 2010; Marino et al. 2012; Beca et al. 2013; Bertholdt et al. 2014; von Rhein et al. 2014; Khalil et al. 2016; Marelli et al. 2016).

Paroxysmal Episodes in Congenital Heart Disease

Paroxysmal episodes associated with congenital heart disease include syncope, seizures, strokes (see Strokes section), and Fallot attacks.

Cardiac syncope can occur with congenital (or acquired) conditions that obstruct left sided outflow, such as hypertrophic cardiomyopathy or aortic stenosis, or that cause cardiac conduction defects, such as Ebstein anomaly. Most cardiac syncope are due to dysrhythmias, either supraventricular or ventricular, which are not associated with structural defects: these are discussed in Chapter 16. As some causes of cardiac syncope carry a risk of sudden death, especially with exertion, exertion-related syncope needs urgent cardiological assessment. Nocturnal syncope is another suggestive symptom.

Epileptic seizures can occur due to an underlying genetic aetiology or cortical malfunction, such as some of those listed in the Cognitive and Motor Development and Heart Malformations section, or as discussed below in association with stroke or abscess and postoperatively.
In young children with right sided outflow obstruction and ventricular septal defects, such as Tetralogy of Fallot, hypercyanotic spells occur as paroxysmal episodes where a child cries, becomes more deeply cyanosed and then becomes limp. Precipitants include exertion, feeds and bowel movement. When severe, convulsions and death can ensue while prolonged attacks may risk hypoxic-ischaemic damage. The mechanism is unclear. Acute management includes oxygen, the knee-chest position, morphine and beta-blockade.

**Strokes**

Congenital heart disease is associated with strokes though embolic, thrombotic or vasculopathic mechanisms, with embolic the commonest. While strokes are most frequent after surgical interventions (below), non-operated patients are also at risk, albeit less so. Emboli can be thrombus of cardiac origin, tissue from atrial myxoma, or valvular material. Children with untreated cyanotic heart disease and right-to-left shunts are at particular risk of stroke, both arterial and venous, but the incidence has declined since earlier intervention has become the norm. Most occurred in infants, with iron-deficiency anaemia and hypoxaemia as risk factors for large vessel arterial stroke, while polycythaemia was a contributor to venous stroke in older children. Most children present with acute motor deficit but aphasia or hemianopia can occur. Subclinical strokes are increasingly recognised (Phornphutkul et al. 1973; Block et al. 2010).

Coarctation of the aorta and aortic stenosis are particularly associated with vasculopathies such as moyamoya. In theory, hypertensive haemorrhagic stroke is a risk in untreated coarctation, but this appears unusual. The role of a patent foramen ovale in permitting paradoxical venous embolic stroke is still controversial (see Chapter 15).

**Brain Abscesses**

These are discussed in Chapter 11. Congenital heart disease, either directly or secondarily to endocarditis, is an important predisposing factor for cerebral abscess in many but not all series. Presenting symptoms can include fever, headache and other symptoms of raised intracranial pressure, and focal signs including seizures. Papilloedema is of little value in patients with cyanotic heart disease, because retinal vessels are frequently engorged and tortuous with blurring of the disc margins. Treatment is based on prospective studies but there is no high level evidence. No current outcome data specific for congenital heart disease is available (Goodkin et al. 2004; Özsürekci et al. 2012; Felsenstein et al. 2013; Lumbiganon and Chakiptipinyo 2013).

**NEUROLOGICAL COMPLICATIONS OF SURGERY FOR HEART DISEASE**

Catheter studies and surgical interventions, whether palliative or corrective, carry neurological risks. These are also affected by the complexity of the surgery, its duration, age at surgery and the child’s pre-operative state.

In children, the main immediate neurologic risk from cardiac surgery is a post-bypass encephalopathy which may be associated with multi-organ involvement. The mechanism is complex, with hypoxia-ischaemia, thrombosis, embolism, metabolic, inflammatory and haematological derangements all possible contributors. The multi-organ component can make postoperative management more difficult; for example, due to problems with fluid and electrolyte control. Various controlled trials of intra-operative management have sought to reduce the risk, with some success, but the outcome is still variable, probably partly influenced by the pre-existing condition of the child. As with all sick children, critical illness neuropathy and myopathy are also possible (Dominguez et al. 2007; Nelson et al. 2008).

A specific form of postoperative encephalopathy with chorea beginning in the first 2 weeks after surgery was recognised as a complication soon after bypass surgery was introduced, and appeared to be related to aspects of surgery such as deep hypothermia and circulatory arrest. The outcome varied but in older children especially persisting chorea and intellectual deficits were frequent (du Plessis et al. 2002).

Focal insults are also important in the immediate postoperative period, when the risk of arterial and venous stroke is highest. Clinically overt strokes have an incidence of less than 1% overall, but routine pre- and postoperative MRI in neonates with more complex disorders show an incidence of up to 9%. Balloon atrial septostomy for transposition of the great arteries may be a risk factor for MRI detected stroke in neonates. Prosthetic replacement valves have a persisting association with stroke. Postoperative stroke is associated with a poor prognosis: in one series only 14% had a normal outcome (McQuillen et al. 2007; Domi et al. 2008; Roach et al. 2008; Block et al. 2010) (Fig. 27.4).

In neonates with complex heart disease requiring bypass surgery, and in those receiving palliation with Blalock-Taussig shunts, MRI can demonstrate new white matter signal changes postoperatively but as these may later resolve their significance.
is currently unclear. Post-mortem studies can show periven- 
tricular leukomalacia or gliosis (Kinney et al. 2005; McQuillen 
et al. 2007; Marino et al. 2012; Beca et al. 2013).

Spinal cord stroke can also occur, in particular with surgi-
ical correction of coarctation, probably by an embolic process 
via the artery of Adamkewicz. Clinically, motor and spheric-
ter signs predominate, but dorsal column function can be 
relatively preserved. There can also be better recovery of 
sensory than motor function.

Seizures, both clinical and electrographic, are seen in 
4–21% postoperatively (‘post pump seizures’), with the lower 
incidence in children with Tetralogy of Fallot and the higher 
those in those with hypoplastic left heart syndrome or an inter-
rupted arch. Other factors include the presence or absence 
of a recognised genetic syndrome and the duration of car-
diopulmonary bypass. Treatable metabolic and toxic causes, 
such as hypoglycaemia, electrolyte disturbance, and drug 
toxicity, should be excluded, especially if associated with an 
cephalopathy: for example, some cardiopulmonary solutions 
are associated with hyponatraemia and seizures. Stroke, both 
haemorrhagic and thrombotic, is another possible cause.

Treatment follows standard guidelines for acute seizures, but 
needs to allow for possible drug accumulation if hepatic or 
renal insufficiency is present. The neurodevelopmental out-
come is poorer in neonates with postoperative seizures than 
those without (Rappaport et al. 1998; Clancy et al. 2003; 
Dominguez et al. 2007; Kim et al. 2011; Gaynor et al. 2013).

**Late Sequelae of Cardiac Surgery**

The neurocognitive effects of surgery itself are difficult to disen-
tangle from the pre-operative factors discussed above, includ-
ing the nature of the underlying condition. Newly acquired 
motor deficits and later epilepsy are the most clear cut, but 
intellectual, learning and behaviour disabilities are also very 
important. The longer term outcomes of an acute postopera-
tive encephalopathy vary markedly, but in general the longer 
the encephalopathy lasts the more worrying the prognosis. 
As well as seizures, other proxy outcome measures are being 
sought so that the effects of interventions can be assessed more 
rapidly than through waiting for assessments at school age or 
later (Bellinger et al. 1995; Dominguez et al. 2007; 

**NEUROLOGICAL COMPLICATIONS OF 
ACQUIRED HEART DISEASE**

Viral myocarditis and rheumatic carditis can also be com-
icated by embolic stroke, with case series reporting risks 
of 4–12%. Many forms of congenital heart disease, valvular 
disease including prosthetic replacement valves, rheumatic 
carditis and indwelling catheters are risk factors for bacterial 
endocarditis, which in children has a 4–20% reported risk of 
stroke. In one case series, more than half of those with strokes 
due to bacterial endocarditis were left with long-term deficits.

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<td>Yes</td>
<td>Dilated</td>
</tr>
<tr>
<td>Andersen syndrome</td>
<td>Yes</td>
<td>Hypertrophic</td>
</tr>
</tbody>
</table>

In adults bacterial endocarditis can lead to meningitis, abscess, 
and myotic aneurysms, but in children the magnitude of these 
risks is unclear (Ferrieri et al. 2002; Roach et al. 2008; 
Venkatesan and Wainwright 2008; Murdoch et al. 2009; 

**CARDIOLOGICAL COMPLICATIONS 
ASSOCIATED WITH NEUROLOGICAL 
DISORDERS**

A number of genetic, metabolic, storage, and neuromuscular 
disorders are associated with cardiomyopathy and/or conduc-
tion defects. Some of the more frequent are listed in Table 27.3. 
The neurological features are discussed in the relevant 
chapters. In many, the cardiac aspect is a potentially life-limiting 
feature, so routine cardiac monitoring is a standard part of 
long-term management. As well as causing cardiac symptoms, 
dilated cardiomyopathy has a 6% risk of stroke. Finally, both 
chronic respiratory failure, due for example to a neuromuscu-
lar condition, and neuromuscular scoliosis can be associated 
with pulmonary hypertension and subsequent right ventric-
ular dysfunction (Hermans et al. 2010; Finsterer et al. 2012).
Pulmonary diseases and other ventilatory problems can affect the CNS through intermittent or chronic hypoxia, carbon dioxide retention, or both. A critical review of the effects of hypoxia, which included cardiac as well as respiratory causes such as sleep disordered breathing, asthma, chronic ventilatory impairment and respiratory instability, concluded that there was evidence of adverse effects on development, behaviour and academic achievement at all ages except for preterm infants. However, the first two conditions accounted for the majority of the evidence and confounding factors are present in both. Blood carbon dioxide levels also have well recognised effects on cerebral perfusion and intracranial pressure (Bass et al. 2004; Lim and Lin 2009).

In addition, chronic bronchiectasis due to conditions such as immunological dysfunction or cystic fibrosis is a recognised risk factor for brain abscess. Malabsorption in cystic fibrosis, especially in association with biliary disease, can lead to undernutrition (discussed in the Protein Energy Undernutrition section), in particular vitamin E deficiency. Mutations in the NKX2-1 gene (see Thyroid section) can cause respiratory symptoms such as surfactant-deficient term neonatal respiratory distress syndrome, and later in childhood recurrent infections and asthma.

Conversely, acute and chronic ventilatory disorders are associated with a number of central or peripheral motor disorders as well as structural or functional brainstem disorders. A weak cough can also lead to retained secretions and an increased risk of infection. In addition, recurrent or chronic aspiration with symptoms such as cough, wheeze and collapse/consolidation can occur in children with neurological disorders and an ‘unsafe’ swallow or gastro-oesophageal reflux disease (Proesmans et al. 2014).

**INTERMITTENT OR CHRONIC HYPOXIA AND CARBON DIOXIDE RETENTION**

From a neurological perspective several conditions need to be considered.

Sleep disordered breathing, including obstructive sleep apnoea, may affect school performance. Children with Down and Prader-Will syndromes are at an increased risk (RCPCH 2009).

Acute mountain sickness can occur in over 20% of children moving from low to high altitude. Symptoms comprise headache, fatigue, nausea, dizziness, and sleep disturbance. In most, symptoms resolve spontaneously or after treatment with hydration, analgesia and preventing further ascent. In a small number of untreated patients, cerebral oedema can develop with symptoms of confusion and ataxia progressing to coma. The mechanism is unclear but hypoxia is presumed to play a role. Treatment includes urgent descent, dexamethasone and oxygen (Imray et al. 2011; Rexhaj et al. 2011).

Carbon monoxide poisoning with acute severe tissue hypoxaemia also causes an acute encephalopathy, sometimes with motor or central and peripheral visual deficits, that may be delayed and transient. Initial symptoms include confusion, dizziness, seizures and coma. Papilloedema and retinal haemorrhages can occur. Neuroimaging typically shows basal ganglia involvement, especially affecting the globus pallidus, but additional cortical and cerebellar changes are reported including laminar and focal infarctions. Survivors can have a variety of neurocognitive and psychiatric sequelae (see Chapter 13) (Hon et al. 2006; Velioglu et al. 2013).

Idiopathic congenital central hypoventilation syndrome (Ondine’s curse) is a rare condition with severe hypoventilation during sleep associated with a range of genetic causes. These include neurocristopathies such as Hirschsprung disease (Haddad syndrome) and neuroblastoma. Autonomic and cognitive dysfunction can be associated (OMIM 209880).

Acute neuromuscular weakness due to anterior horn cell problems, classically polio, neuromyopathies such as Guillain–Barré syndrome, myasthenic crisis and acute myopathies with or without rhabdomyolysis are well recognised risk factors for acute respiratory insufficiency. Difficulty weaning from ventilatory support after a period of intensive care can be due to critical illness neuropathy or myopathy. Risk factors include multisystem involvement, the need for renal dialysis, and sepsis. It is an important differential if assessing for possible brain stem death. While clinically overt cases are infrequent, neurophysiological studies show a degree of neuropathic dysfunction in more cases (Williams et al. 2007).

Hypventilation is also an important complication of chronic conditions causing severe progressive neuromuscular weakness and some specific ones such as spinal muscular atrophy with respiratory distress (SMARD). Hypoventilation is intermittent at first, mainly associated with REM sleep, so initial symptoms of headache, nausea and fatigue due to carbon dioxide retention and hypoxaemia occur on waking. As the severity worsens, anorexia, fatigue and listlessness develop. Acute on chronic respiratory failure can be triggered by aspiration or intercurrent infection. Prophylactic monitoring, assessment and management involve specialist respiratory care, as well as a number of ethical issues, and are discussed in several guidelines (Bushby et al. 2010; Hull et al. 2012; Gray et al. 2013).

Children with chronic lung disease due to preterm birth are also at risk of hypoxia and carbon dioxide retention. Adverse neurodevelopmental outcomes often have additional non-respiratory causes related to preterm birth. In addition, although the incidence of broncho-pulmonary dysplasia is unchanged, its character and pathophysiology appears to differ since the introduction of surfactant and newer ventilatory techniques. In the ‘old’ form both progressive neurological impairment and a specific self-limiting movement disorder were reported. The latter began at 3 months of age with prominent tongue, facial and distal limb dyskinesias. Chronic
lung disease is associated with progressive white matter injury in preterm infants, which may not have clinical effects, but here infection may play an important role (Ellison and Farina 1980; Glass et al. 2008; Mosca et al. 2011).

COMPLICATIONS OF EXTRACORPOREAL MEMBRANE OXYGENATION

In neonates and children with cardiorespiratory failure, ventilatory and intensive circulatory support may not be sufficient, in which case extracorporeal life support, mainly extracorporeal membrane oxygenation (ECMO), can be indicated. In neonates, congenital diaphragmatic hernia, meconium aspiration syndrome and sepsis are the commonest reasons, while in older age groups there is a wider range, with seasonal variations due to causes such as influenza. The children are usually extremely ill with multiple additional problems including sepsis, haematological and metabolic derangements which already place them at increased risk of neurological sequelae. Nevertheless, survival rates approximate 80%. Veno-arterial ECMO requires ligation of the right internal jugular vein and the right carotid artery, together with heparinisation. Seizures, focal ischaemia and intracerebral haemorrhage are the major acute risks, occurring in 5–20%, all as might be expected associated with a poorer outcome. During ECMO, EEG monitoring can show a range of focal or diffuse abnormalities including status epilepticus. Of the survivors, 15–25% have major neurological impairments, including intellectual disability, epilepsy and quadriplegia, while up to 50% may have later learning and behaviour difficulties. In some but not all series, more lesions occur in the right hemisphere. Veno-venous ECMO without carotid artery ligation may have a lower overall risk, but direct comparison is difficult (Karimova et al. 2009; Dalton and Butt 2012; Mehta and Ibsen 2013; de Mol et al. 2013).

APNOEIC EPISODES AND APPARENT LIFE-THREATENING EVENTS

Apparent life-threatening events are defined as ‘an episode that is frightening to the observer and that is characterised by some combination of apnoea (central or occasionally obstructive), colour change (usually cyanotic or pallid), marked change in muscle tone, choking or gagging’. Apnoeic attacks mainly occur in neonates and young infants, with a wide differential diagnosis, mostly respiratory, cardiac or gastro-oesophageal reflux related. Recognised neurological causes are less common, but include brainstem disorders and epilepsy (Table 27.4). Epilepsy can present with pure apnoeas, typically without bradycardia, in the neonatal period, or less frequently as a manifestation of focal epilepsy in infancy. Causes can include temporal lobe tumours, KCNQ-related epilepsy, migratory partial seizures and 1p36 deletion syndrome. Apnoeas in neonatal hyperekplexia can be life threatening and can be aborted by neck flexion (Watanabe et al. 1982; Ramelli et al. 1998; RCPCH 2009; Kanabar et al. 2012; Thomas et al. 2013; Allen et al. 2014).

HYPERVERTILATION

Hyperventilation attacks are functional events triggered by psychological factors. Many are asymptomatic but in some symptoms of dizziness develop, while in a small number tetany develops due to a lowered ionised calcium level. Symptoms of dizziness frequently occur with hyperventilation performed during EEG recordings. Acute symptoms respond to rebreathing, which is also a diagnostic pointer, while further treatment may require psychological referral or the teaching of specific breathing exercises.

A number of conditions with neurological features are associated with intermittent hyperventilation or variable respiratory patterns, including Rett, Pitt-Hopkins and Joubert syndromes.

HEPATIC DISEASE

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy constitutes the end stage of acute or chronic liver disease and culminates in hepatic coma. In adults but not in children, the diagnosis of acute severe hepatic failure requires the presence of an acute encephalopathy. In many countries the most important cause is acute viral hepatitis, with a risk of encephalopathy of up to 72%. In some series, infants form the largest age group. Hyperammonaemia is suggested to be a pathogenetic factor, with astrocytes as particular

Table 27.4  Neurological causes of intermittent apnoea

<table>
<thead>
<tr>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Arnold-Chiari malformations 1 and 2</td>
</tr>
<tr>
<td>Joubert syndrome</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
</tr>
<tr>
<td>Glycine encephalopathy</td>
</tr>
<tr>
<td>Biotin deficiency</td>
</tr>
<tr>
<td>Leigh syndrome</td>
</tr>
<tr>
<td>Late infantile remethylation defects</td>
</tr>
<tr>
<td>Aromatic amine deficiency</td>
</tr>
<tr>
<td>Glut1 deficiency</td>
</tr>
<tr>
<td>Epileptic seizures</td>
</tr>
<tr>
<td>Hyperekplexia</td>
</tr>
<tr>
<td>Rett syndrome (in males)</td>
</tr>
<tr>
<td>Spino-cerebellar ataxia type 2</td>
</tr>
<tr>
<td>Familial infantile myasthenia (RAPSN or CHAT)</td>
</tr>
</tbody>
</table>

RAPSN, receptor associated proteins of the synapse; CHAT, choline acetyltransferase.
targets. However, the underlying aetiology or complications, including metabolic, infectious or autoimmune disorders, gastrointestinal haemorrhage and drugs, can also contribute to the neurological features.

The onset of hepatic encephalopathy is sometimes fulminant but it is more often heralded by malaise, anorexia and vomiting. Disorders of consciousness are the principal symptoms. Disorientation, anxiety, depression and slurred speech appear first. They are rapidly followed by drowsiness, lethargy and inappropriate behaviour. Asterixis or ‘flapping tremor’ may be an early feature. Extrapyramidal rigidity and choreic movements are frequent in children. Ataxia, seizures, myoclonus and hyperventilation with resulting alkalosis frequently develop in advanced stages. Decerebrate posturing may occur in the terminal phase. In adults various scales have been devised to assess the degree of encephalopathy, most often modified forms of the West Haven criteria, which can also be applied to older children (Table 27.5). In younger children and infants, paediatric scales are available, but differ between authors. When severe a paediatric coma scale can also be used, such as the James scale. The EEG often shows diffuse bursts of high-voltage slow-wave activity and sometimes triphasic spikes, epileptiform discharges and clear electroclinical seizures. In acute failure EEG abnormalities correlate with the outcome. Neuroimaging is usually normal. The course may be rapidly lethal, associated with severe cerebral oedema, or fluctuate considerably, and symptoms may be rapidly reversible if the course of the liver disease is favourable. Urgent assessment for possible liver transplantation is the most important aspect of treatment in those with severe encephalopathy. Other supportive measures include management of raised intracranial pressure and seizures, reduction of ammonia production, treatment of sepsis, and dose adjustment of drugs metabolised by the liver. A substantial minority also develop renal failure (Lee et al. 2005; Squires et al. 2006; Arya et al. 2010; Bravo et al. 2012; Hussain et al. 2014).

In adults with chronic liver failure, varying degrees of cognitive impairment have been well recognised. While there is less data in children, cognitive dysfunction appears equally important and to correlate to duration and severity of liver disease. However, the pattern of dysfunction is complex: for example, those with an early onset may be particularly compromised in terms of perceptual synthesis and psychomotor speed (Stewart et al. 1992; Moser et al. 2013).

In some children a congenital portosystemic shunt, a rare condition characterised by hyperammonaemia, can present with intellectual disability or symptoms of attention-deficit–hyperactivity disorder without other features (Kim et al. 2012).

### ANTICONVULSANT DRUGS AND HEPATIC IMPAIRMENT

Anticonvulsant and other drug-induced hepatopathy is well recognised although rare (see also Chapter 16). While the association with valproate therapy is the best known, equally important relative risks are reported for sulthiame, ethosuximide, phenobarbital, phenytoin and carbamazepine. Jaundice is a frequent clinical feature. Fatal valproate associated hepatic failure is linked with young age, polytherapy, developmental impairment and metabolic disorders including Alper syndrome (see Chapter 9), with a reported risk of up to 1 : 600 in children under 2 years of age, but in recent series this may be lower. Symptoms usually develop in the first months of treatment and include reduced alertness, increased seizures, anorexia, vomiting, jaundice and haemorrhage. Transaminase levels can often be raised in children on valproate treatment and do not correlate to the risk of sudden hepatic failure, so are not a useful warning. Carnitine has been proposed as prophylaxis but its efficacy is not proven. Parents of children treated with valproate should be advised to report any of the symptoms above immediately.

From a wider perspective, acute or subacute encephalopathy can occur in children and adults receiving valproate with or without hyperammonaemia and with or without hepatopathy. Finally, acute pancreatitis is another important complication of valproate therapy, presenting with abdominal pain and vomiting, and confirmed by raised blood levels of exocrine pancreatic enzymes. Most children have normal serum levels. If valproate is re-introduced symptoms are likely to recur (Bryant and Dreifuss 1996; Koenig et al. 2006; Gerstner et al. 2007; Ferrajolo et al. 2010).

### OTHER COMPLICATIONS OF HEPATIC IMPAIRMENT AND ITS TREATMENT

Hepatic impairment can be associated with malabsorption leading to the complications described in the Protein

<p>| Table 27.5 Modified West Haven Criteria for Hepatic Encephalopathy assessment |
|-----------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Grade</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormality detected</td>
</tr>
<tr>
<td>I</td>
<td>Trivial lack of awareness</td>
</tr>
<tr>
<td></td>
<td>Euphoria or anxiety</td>
</tr>
<tr>
<td></td>
<td>Shortened attention span</td>
</tr>
<tr>
<td></td>
<td>Impairment of addition or subtraction</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy or apathy</td>
</tr>
<tr>
<td></td>
<td>Disorientation for time</td>
</tr>
<tr>
<td></td>
<td>Obvious personality change</td>
</tr>
<tr>
<td></td>
<td>Inappropriate behaviour</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence to semi-stupor</td>
</tr>
<tr>
<td></td>
<td>Responsive to stimuli</td>
</tr>
<tr>
<td></td>
<td>Confused</td>
</tr>
<tr>
<td></td>
<td>Gross disorientation</td>
</tr>
<tr>
<td></td>
<td>Bizarre behaviour</td>
</tr>
<tr>
<td>IV</td>
<td>Coma, unable to test mental state</td>
</tr>
</tbody>
</table>

Bajaj et al. (2011).
GASTROINTESTINAL DISORDERS

Most neurological complications of gastrointestinal disorders are secondary to infection, auto-immunity or malabsorption. Acute encephalopathies due to viral gastroenteritis and bacterial enterocolitis are discussed in the Neurological Complications of Acute Gastroenteritis Without Dehydration section. Stroke can be associated with inflammatory bowel diseases including Crohn’s disease and ulcerative colitis. Acute inflammatory polyradiculoneuropathy (Guillain–Barré syndrome), in various forms including the acute motor axonal presentation described in Asia, is strongly associated with Campylobacter jejuni infection.

Conversely, many neurological disorders, both central and peripheral, can be associated with problems along the length of the gastrointestinal tract. Co-ordination of buccal, oesophageal, gastric, intestinal and colonic motor function depends on the central, autonomic and enteric nervous systems and requires normal voluntary and smooth muscle function. The nutritional and respiratory aspects of swallowing difficulties and gastro-oesophageal reflux disease in children with central and peripheral motor disorders are outlined earlier in this chapter. Gastro-oesophageal reflux disease is more prevalent in children with neuro-disability in general and can present with non-specific features such as self-mutilation and agitation, as well as Sandifer syndrome (see Chapter 18); (Gössler et al. 2007). Gastrointestinal dysmotility has a wide range of associations. Recognised neurological ones include mitochondrial disorders (mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome – see Chapter 9), and neuromuscular disorders such as myotonic dystrophy type 1 and Duchenne muscular dystrophy. Symptoms include nausea, vomiting, abdominal pain and constipation. In severe cases intestinal pseudo-obstruction and failure can supervene. Less well studied are the problems in some children with severe hypertonia, where feeding can be very difficult and even if given continuously enterally can be associated with distressing dystonic spasms. Pneumatosis coli can also occur: both it and feeding intolerance may improve after defunctioning ileostomy. As parenteral nutrition has its own complications and costs, management can be very difficult and requires expert gastro-enterological advice. Detailed descriptions, investigation and management are beyond the scope of this chapter (Di Lorenzo and Youssef 2010; West et al. 2016).

GLUTEN ENCEPHALOPATHY

Untreated gluten enteropathy, or celiac disease, can cause neurological effects though the associated undernutrition and micronutrient deficiencies as discussed earlier in the Nutritional Disorders and the Nervous System section. In adults associations have been suggested with epilepsy, ataxia, and neuropathy, through a presumed autoimmune mechanism, but in children the supportive evidence for any of these is weak. There may be a stronger link with headache and fatigue. One child has been reported with multiple episodes of demyelinating encephalitis in whom the recognition and treatment of coeliac disease resulted in neurological cure. In adults, gluten sensitivity, that is, positive antibody titres with or without enteropathy, is also being explored as a possible cause of neurological and psychiatric problems (Hadjivassiliou et al. 2010; Lionetti et al. 2010; Jackson et al. 2012; Terrone et al. 2013; Jorge et al. 2014).

Gluten Enteropathy Associated with Epilepsy and Cerebral Calcification

This rare condition was first described in Italy by Gobbi, where children with intractable epilepsy and cerebral calcification, typically in the parieto-occipital region were found to have gluten enteropathy. If detected and treated early, seizures responded favourably to a gluten-free diet. Subsequent experience has shown that most patients are from Italy, Spain or Argentina and that the epilepsy can vary markedly in severity and drug responsiveness. Dietary treatment does not lead to resolution of the cerebral calcification. Congenital folate malabsorption enters the differential diagnosis (Gobbi 2005; Johnson et al. 2013).

Table 27.6 Conditions with neurological and hepatic impairment

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate dehydrogenase deficiency e2 alpha</td>
</tr>
<tr>
<td>Mitochondrial cytopathies, including Alper syndrome</td>
</tr>
<tr>
<td>Peroxisomal disorders</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
</tr>
<tr>
<td>Niemann-Pick type 3</td>
</tr>
<tr>
<td>Aicardi-Goutiere syndrome and other hereditary inflammatory disorders</td>
</tr>
<tr>
<td>Reye syndrome</td>
</tr>
<tr>
<td>Wilson disease</td>
</tr>
<tr>
<td>Drug therapy</td>
</tr>
</tbody>
</table>

Table 27.6 Conditions with neurological and hepatic impairment

Methods

- Deficiencies of the fat-soluble vitamins D, E and K can lead to neurological complications. Coagulopathy can also complicate hepatic insufficiency due to decreased synthesis of prothrombin.
- A number of neurological conditions are associated with biochemical or more overt features of liver dysfunction (Table 27.6). From experience, some children with raised alanine and aspartate transaminase levels due to muscle disorders may be initially referred to a hepatologist because a muscle origin has not been not considered.
WHIPPLE DISEASE

This rare condition, mostly seen in adults, is caused by *Tropheryma whipplei*, an intracellular micro-organism which causes a histiocytic response. Intrafamilial cases can occur. In order of frequency, the main symptoms are rheumatological, cardiac and neurological. The latter include a variety of cognitive, behavioural and motor manifestations such as oculomasticatory (in particular) or more generalised myoclonus, ataxia and ophthalmoplegia. These are due to multifocal inflammatory lesions throughout the neuraxis which at their most severe cause a necrotising encephalitis. Diagnosis used to depend on small intestinal biopsy but has been replaced by PCR. The condition responds to antibiotic therapy (Lagier et al. 2010; Meunier et al. 2013).

CYCLICAL VOMITING

The pathogenesis of cyclical vomiting is often unclear. Among other possibilities, neurological causes to consider include migraine, fourth ventricular tumours and other brainstem disorders, including a personal case with isolated Alexander disease (see Chapter 10), lymphocytic hypophysitis, and paroxysmal vertigo syndromes such as the episodic ataxias.

INTUSSUSCEPTION

Intussusception is a gastrointestinal emergency classically presenting in infants and young children with abdominal pain, vomiting and blood-stained stools. However, in some infants it may present initially with disturbances of consciousness (obtundation or even coma) that suggest a primary neurological disease. Similar presentations have also been described in children with bowel strangulation or volvulus. Vomiting may be incorrectly thought to have a neurological origin. There is usually a full recovery once the cause is treated. The mechanism is unexplained. These rare examples reinforce the importance of a full history and thorough general examination in all children presenting with acute encephalopathy (Goetting et al. 1990; Pumberger et al. 2004).

RENAL DISEASES

Cerebral symptoms and signs frequently accompany uraemia, although the mechanisms of neurological impairment are poorly understood. However, neurological manifestations of renal disease have considerably decreased in frequency with newer therapies. Some therapeutic procedures, for example dialysis, may have complications mainly due to one specific factor but in most cases the aetiology is probably multifactorial, including factors such as electrolyte disorders, hypertension or neurotoxicity.

PERIPHERAL URAEMIC NEUROPATHY AND MYOPATHY

In children with renal impairment weakness, falls and exercise limitation can have multiple contributing factors, including disuse, anaemia, vitamin D deficiency, neuropathy and myopathy.

In adults, chronic renal failure is associated with clinical polyneuropathy in half or more of all patients. In children, clinically apparent neuropathy is not widely reported but neurophysiologic studies have still shown a significant subclinical prevalence of up to 76%. As in other toxic or metabolic neuropathies, when symptomatic the neuropathy can be painful or uncomfortable, with symptoms of tingling, electric shocks, burning and hypeaesthesia, especially in the feet. Leg cramps are a characteristic early symptom. Typical clinical findings are mainly sensory with vibration impairment an early feature. Neurophysiological findings indicate a predominantly axonal sensorimotor form affecting large and small fibres. The facial nerve is most likely to show conduction disturbances. Autonomic involvement can also be detected by specific tests but again is usually asymptomatic. Nerve biopsy shows axonal loss.

In adults, even in severe cases, successful transplantation is curative. Dialysis may prevent worsening but does not lead to improvement. Symptoms may be helped by treatment with drugs such as gabapentin or carbamazepine. Possible contributory nutritional factors should also be addressed.

Mononeuropathies are also described in association with arteriovenous fistulae, including carpal tunnel syndrome and more rarely ischaemic or compressive neuropathies. In addition, mononeuropathies such as facial weakness can be part of a renal polyneuropathy. Facial nerve palsy can also be associated with arterial hypertension.

Uraemic myopathy is another recognised complication, with muscle biopsy reflecting a variety of myopathic as well as neuropathic features (Mendoza-Guevara et al. 1997; Morgenlander 1997; Pirzada and do Prado et al. 1998; Tory et al. 2001; El-Husseini et al. 2005; Ho et al. 2012).

URAEMIC ENCEPHALOPATHY AND OTHER NEUROLOGICAL ASSOCIATIONS

Children with acute or chronic renal failure can develop acute or chronic encephalopathy. This usually manifests in a chronic fashion as a variable degree of impairment of cognitive function and behaviour, but can present acutely. It is recognised prior to or during dialysis, when it is termed uraemic
or dialysis encephalopathy respectively, but both types have overlapping and probably multifactorial causes.

Prior to dialysis, a substantial minority of children with mild to moderate renal impairment show reductions in measurements of intelligence, memory, concentration, executive function and academic achievement that correlate with severity and duration of renal impairment. Restless leg syndrome, a well-recognised association in adults, is now being reported in children. The differential includes direct effects from the metabolic disturbance, cerebral effects from the underlying pathology, toxins including drugs and aluminium, nutritional deficiencies, and hypertensive encephalopathy. Direct effects are thought to be due to the accumulation of toxic metabolites that are normally removed by the kidney, although no specific candidates have been confirmed. Acute symptoms respond to dialysis, over a period of hours to days. Prior to dialysis protein restriction may also help. Infants with chronic renal failure have traditionally shown a poorer prognosis than older children in longer-term cognitive outcomes. This was suggested to be due to other, possibly genetic, conditions affecting both the brain and kidney, but recent improvements in outcome with more immediate management imply a more direct effect (Rotundo et al. 1982; Gerson et al. 2006; Slickers et al. 2007; Hooper et al. 2011; Wong et al. 2012; Johnson and Warady 2013; Riar et al. 2013).

Some underlying pathologies, especially genetic and vascular, can involve both the kidney and the brain. Genetic conditions such as Smith-Lemli-Opitz or Lowe syndrome associate renal problems, although not usually renal failure, with microcephaly, cerebral dysgenesis, seizures, learning impairment, and behavioural concerns. Cystinosis is an important cause of renal failure but the neurological effects mostly appear in adulthood. Other condition such as Von-Hippel-Landau, polycystic renal disease, and tuberous sclerosis are not usually associated with impaired renal function. Acquired causes include haemolytic-uraemic syndrome and other vasculopathies.

In addition, a large number of genetic conditions associate renal and hearing impairment: examples include some mitochondrial cytopathies, infantile Bartter syndrome and recessive Alport syndrome. Acquired causes include drugs such as aminoglycosides.

Haemolytic-uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura are both thrombotic microangiopathies most frequently due to abnormal regulation of the complement alternative pathway. They are differentiated by ADAMTS13 auto-antibodies. Thrombotic thrombocytopenic purpura (TTP) is discussed below. Most childhood cases of HUS follow gastroenteritis associated with Shiga-toxin producing *Escherichia coli* 0157:H7. Other possible causes (‘atympical HUS’) are age related and include genetic factors, a variety of other infective agents including *Streptococcus pneumoniae*, dysimmune states, certain drugs and a disorder of cobalamin metabolism. While the presenting features are usually renal, neurological complications and sequelae occur in an important minority. Acute symptoms include severe headache, seizures, reduced level of consciousness and focal signs such as cortical visual impairment, hemiparesis or extrapyramidal disorders. MRI in the acute phase shows that all parts of the brain can be involved, but there is a poor correlation to outcome unless haemorrhage occurs. In some, the MRI pattern reflects arterial hypertension (see below). Depending on the aetiology and severity, treatment with fresh frozen plasma, plasma exchange, and eculizumab, a C5 blocking monoclonal antibody, are all therapeutic options. Some children can survive with persisting motor and intellectual deficits (Steinborn et al. 2004; Yamamoto et al. 2009; Nathanson et al. 2010; Loirat and Frémeaux-Bacchi 2011; Donnerstag et al. 2012; George and Nester 2014).

Lupus erythematosus is the vasculopathy most likely to have renal and neurological effects, with a wide variety of possible manifestations including psychiatric presentations, headache, seizures, stroke, movement disorders especially chorea, neuropathies which are often focal and myositis. Other vasculitides such as Henoch-Schoenlein purpura can more rarely have a similar range of neurological manifestations. In both, systemic hypertension can cause its own neurological and imaging features (Bader-Meunier et al. 2005; Hiraki et al. 2008; Garzoni et al. 2009).

Endogenous toxins are discussed above, but exogenous ones, especially drugs normally excreted by the renal route such as penicillin, can also affect the brain if retention causes toxic levels. In neurology this particularly applies to anticonvulsants such as topiramate, gabapentin, pregabalin and vigabatrin, which are largely excreted by the renal route, while others such as levetiracetam, zonisamide, lacosamide, ethosuximide and felbamate still need dosage adjustments. In addition, administration of aluminium, especially with citrate compounds, was an important cause of encephalopathy until its neurotoxicity was recognised. In the older literature progressive symptoms were reported, typically starting with motor impairment, extensor plantar responses and ataxia or dysmetria, followed by myoclonus and seizures, dementia and bulbar dysfunction. In adults, additional symptoms include a variety of movement disorders such as tremor, asterixis and chorea, and there was often a fluctuant pattern. The myoclonus responded to benzodiazepines. Many such cases were probably due to brain aluminium accumulation. Similar aluminium neurotoxicity has been demonstrated in preterm children without overt renal impairment (Foley et al. 1981; Sedman et al. 1984; Bishop et al. 1997).

Acute hypertension can present with headache, seizures, reduced level of consciousness, subarachnoid haemorrhage and visual symptoms. On fundoscopy ateriovenous nipping, retinal haemorrhages and papilloedema may be present. While clinical stroke can occur, in contrast to adults, hypertension is not a common cause of intracerebral haemorrhage in children. Both coarctation of the aorta and polycystic renal disease can associate hypertension with intracranial aneurysms but the latter are not usually symptomatic until early adulthood. The symptoms and pathological features of hypertensive
encephalopathy in children have been known for decades but the characteristic association with posterior reversible encephalopathy (PRES) was not recognised until the advent of neuroimaging, especially MRI. This condition comprises selective white matter signal change classically involving the parieto-occipital region, which resolves once the cause is treated. While most often due to acute hypertension it can have other causes, especially anti-neoplastic agents. With experience it is now recognised that PRES is not always posterior nor always reversible: frontal white matter involvement is frequent, especially the dominant superior sulcus; there can be a holohemispheric watershed pattern and appearances may be asymmetric. Some children with oncological causes can develop focal haemorrhages or coning, and residual damage especially laminar necrosis can be seen. Most children recover completely after appropriate treatment but some can have persistent deficits (van Vught et al. 1976; Hinchey et al. 1996; Onder et al. 2007; Roach et al. 2008; Chen et al. 2013; Cordelli et al. 2014) (Fig. 27.5).

Chronic arterial hypertension, which may be associated with previously unrecognised renal impairment, is an important differential diagnosis of migraine. Once diagnosed, careful tapering of the blood pressure is vital as over-rapid reduction can lead to blindness due to optic nerve infarction (Browning et al. 2001).

### COMPLICATIONS OF TREATMENT OF CHRONIC RENAL FAILURE

The onset of a reduced level of consciousness in a child during or soon after haemodialysis requires standard assessment for causes of an acute encephalopathy, including vascular and electrolyte disorders. One important although unusual possibility is the dialysis dysequilibrium syndrome, particularly in younger children, which appears to be related to cerebral oedema secondary to osmotic shifts between the brain and blood. Milder forms present with headache, restlessness, nausea and muscle cramps, but more severe features can include myoclonus, seizures, confusion and coma. It is more severe and frequent if the initial blood urea is very high and the risk is reduced with a slower correction of uraemia. Adding an osmotic agent such as mannitol also helps avoid the problem. Alternatively haemofiltration might be preferable as initial treatment since this also results in a slower osmotic shift. As there is no specific test it is a diagnosis of exclusion (Zepe-da-Orozco and Quigley 2012).

Another dialysis-specific cause is aluminium toxicity. In haemodialysis this is linked to the aluminium concentration of the dialysis fluid, but acute cases can follow oral administration. Symptoms included personality changes, dysarthria, apraxia of speech, myoclonus and seizures. The EEG shows slowing of background tracings and multiple paroxysms. Chronic dialysis encephalopathy due to aluminium toxicity has now largely disappeared following appropriate water treatment (Schréder et al. 1983).

Many children with chronic renal conditions have evidence of undernutrition. Classically, Wernicke encephalopathy could occur in children on dialysis, although awareness now usually leads to prevention (Worsley et al. 1965; Castillo et al. 2012).

Haemodialysis can also be associated with chronic subdural haematoma.

The cognitive impairment associated with uraemia may not completely resolve with dialysis and further improvement can occur following successful transplantation (Moser et al. 2013).

### REJECTION ENCEPHALOPATHY

Neurological disorders post transplantation are discussed in the Neurological Complications of Allogeneic Bone Marrow and Organ Transplantation section. Especially in the first few months after transplantation, acute rejection episodes can be complicated by an acute encephalopathy with headaches, seizures and reduced level of consciousness. The cause is uncertain. Treatment is symptomatic and the outcome is usually good. It is important to recognise that this syndrome is not due to disturbances in electrolytes, hypertension, fever or steroids, so steroid treatment may be continued.
Several bone disorders may be associated with neurological symptoms and signs, through various mechanisms that include compression of nerves at the skull base, venous compression with resulting hydrocephalus, narrowing of the foramen magnum or of the vertebral canal with resulting compression of the medulla, spinal cord or nerve roots, and craniosynostosis (Saland 2004). Several of these disorders such as achondroplasia and osteogenesis imperfecta are covered in Chapter 6.

Fibrous dysplasia of bone is characterised by proliferation of fibrous tissue in osseous tissue due to a post zygotic activating mutation in the GNAS1 gene. Onset is in childhood or adolescence in over half the cases. Up to 34% of cases may exhibit the association of café-au-lait skin pigmentation and endocrine disorders (McCune Albright syndrome; OMIM 174800). Craniofacial involvement can lead to pain and cranial nerve compression (Wilson and Hall 2002; Lee et al. 2012).

Osteopetrosis, due to osteoclast dysfunction, can be dominant or recessive. The latter has at least eight recognised genetic causes and is usually more severe, especially in its infantile form. Infants present with feeding difficulties secondary to choanal atresia and later develop compressive cranial neuropathies which can cause visual impairment, nystagmus and strabismus; hearing loss which affects nearly 80%; facial paralysis, anosmia and trigeminal neuropathy. Depending on the genetic cause, intellectual disability can be mild or severe. These children develop extra-medullary haematopoiesis with hepatosplenomegaly and eventual marrow failure. Bone marrow transplantation has good results if the donor is well matched but not otherwise.

Carbonic anhydrase II deficiency also causes osteopetrosis with basal ganglia calcification and renal tubular acidosis. The osteopetrosis, but not the other manifestations, responds to transplantation (Sly et al. 1983; Gerritsen et al. 1994; McMahon et al. 2001; OMIM 259700).

## HEREDITARY HAEMOGLOBINOPATHIES

### Sickle Cell Disease

The major neurological complication of sickle cell disease is the much increased risk of ischaemic stroke, both overt and subclinical. In overt stroke, symptoms occur in isolation or during a sickle crisis. Risk factors include anaemia, nocturnal hypoxaemia, arterial hypertension, elevated flow rate on transcranial Doppler in the anterior cerebral artery especially, and moyamoya syndrome. The risk is highest in the 2–5 year age group. Large vessel disease affecting the carotid circulation mainly leads to large middle cerebral artery territory infarcts, or moyamoya. Smaller infarcts involve the basal ganglia or deep white matter. Treatment includes hydration and exchange transfusion.

Depending on the definition used and the imaging technology, subclinical strokes occur in over a third of children by early adolescence and are associated with a significantly increased risk of clinically overt stroke. The risk of intracerebral haemorrhage is also significantly raised. This is more frequent in young adults and is associated with large vessel vasculopathy or sinus venous thrombosis. Similarly subarachnoid haemorrhage can occur, especially in adolescents, either of aneurysmal origin, or in association with sinus venous thrombosis or moyamoya. Spinal infarcts have also been reported.

Current management recommendations include regular screening by transcranial Doppler, and transfusions for secondary stroke prevention, but their effectiveness is not fully proven. Hyperventilation during EEG recording should be avoided in patients with sickle cell disease as it may result in neurological impairment precipitated by the reduction of blood flow that occurs during the test. Children with sickle cell trait (heterozygotes) have a low incidence of neurological accidents, of the order of 6%.

Academic difficulties, cognitive deficits and behavioural problems are common in children with sickle cell disease. However, at present it is difficult to disentangle the roles of biological and environmental factors present in most affected children.

In adults, leuкоencephalopathy is increasingly recognised, and has been described acutely in children in association with acute chest crisis. Because of auto-splenectomy the risk of infection with encapsulated bacteria such as pneumococcus, including meningitis, is increased. Headaches and migraine are also prevalent in children with sickle cell anaemia, and may be undertreated (Lee et al. 2002; Henderson et al. 2003; Roach et al. 2008; DeBaun et al. 2012; Wang and Dwan 2013; Dowling et al. 2014).

### Thalassemias

Untreated beta thalassaemia major is associated with cerebral sinus venous thrombosis, due to the resulting anaemia. As with sickle cell anaemia, it is also linked to subclinical or silent cerebral infarcts, as is haemoglobin SC (HbSC) disease, but the risk factors and effects have not been studied in such detail. There are also some reports of moyamoya or silent clinical infarcts in the milder form, beta thalassaemia intermedia, particularly in adulthood. Very rarely in severe anaemia, extra-medullary haematopoiesis can cause spinal cord compression. Headache and syncopal symptoms linked to anaemia are also reported. A mild peripheral neuropathy causing sensory symptoms, cramps, myalgia and weakness has been described,
predominantly in young adults (Logothetis et al. 1972; Papanastasiou et al. 1991; Zafeiriou et al. 2006; Roach et al. 2008; Leblebisan et al. 2012; Haghpahan and Karimi 2012). Alpha thalassaemia (HbH) disease itself is not usually linked to neurological problems except those secondary to severe chronic anaemia. However, intellectual disability can be associated with alpha thalassaemia through two recognised genetic mechanisms. In the X-linked alpha thalassaemia mental retardation syndrome, due to mutations in the ATRX gene, affected males have severe intellectual deficits, dysmorphic features, genital anomalies and alpha thalassaemia. Up to one-third have seizures. More rarely, a contiguous gene deletion affecting the alpha thalassaemia gene locus on chromosome 16 can also associate variable degrees of intellectual problems with a variety of dysmorphic features, microcephaly, genital anomalies in males and congenital talipes equino-varus (OMIM 300032 and 141750).

OTHER ANAEMIAS

All anaemias may be accompanied by neurological symptoms such as irritability, listlessness and fatigue. A cranial bruit can be heard in some patients. Iron deficiency is the most common cause of anaemia worldwide, and has several neurological associations, discussed in the Micronutrient Disturbances section.

Several hereditary haemolytic anaemias also have neurological associations. However, the most common, glucose-6-phosphatase deficiency and pyruvate kinase deficiency, do so as possible contributors to bilirubin encephalopathy in neonates. Similarly, hereditary spherocytosis and elliptocytosis are not usually associated with neurological issues, although spinal cord disease has been reported in hereditary spherocytosis (McCann and Jacob 1976).

Among anaemias due to deficiency of glycolytic enzymes, phosphoglycerate kinase deficiency is an X-linked condition which can cause myopathy, myoglobinuria and at times central problems such as hemiplegic migraine and seizures (OMIM 311800). Triosephosphate isomerase deficiency can have widespread neurological involvement with both central and peripheral motor abnormalities, including pyramidal and extrapyramidal features such as spasticity, tremor, dyskinesia, peripheral neuropathy and myopathy. Early respiratory failure is an important cause of death (OMIM 615512). In a single case, deficiency of glucose phosphate isomerase, which catalyses the interconversion of glucose-6-phosphate and fructose-6-phosphate, caused myopathy, sensory ataxia and intellectual disability (Schröter et al. 1985).

Disorders of the gamma-glutamyl cycle can also cause haemolytic anaemia and neurological problems. Gamma-glutamylcysteine synthetase deficiency causes spinocerebellar degeneration and peripheral neuropathy, while glutathione synthetase deficiency with 5-oxyprolinuria causes intellectual disability and central motor disorders such as spasticity and ataxia (OMIM 606857 and 266130).

Other disorders associating anaemia and neurological problems in some cases include Fanconi and Diamond-Blackfan anaemias, with microcephaly and intellectual disability; Wilson disease with haemolytic anaemia, and vitamin E deficiency. In children requiring long-term enteral feeds, some with underlying neurological problems, chronic anaemia can be a sign of copper deficiency.

POLYCYTHEMIA

In children polycythaemia is most commonly seen in neonates, particularly those who are small for gestational age. Most neonates are asymptomatic but some can develop symptoms such as feeding difficulties and jitteriness. Seizures and rarely sinovenous thrombosis are also reported. While an association with an adverse neurodevelopmental outcome is suspected, especially in those with seizures, this has been hard to prove, as confounding factors such as hypoglycaemia may contribute. Partial exchange transfusion does not improve the cognitive outcome and is associated with an increased risk of necrotising enterocolitis (Dempsey and Barrington 2006).

In older children and adults, presenting symptoms can include fatigue, headache and dizziness. Unlike adults, in children the risk of stroke and sinovenous thrombosis does not seem markedly elevated. Some cerebellar haemangiomas such as von Hippel-Landau syndrome can cause polycythaemia due to excess secretion of erythropoietin (Roach et al. 2008; Cario et al. 2009).

ACANTHOCYTOSIS

Neuroacanthocytosis describes a group of genetic syndromes associating neurological features with red cell acanthocytosis. The latter may require special techniques to be revealed on a blood film. The main syndromes are chorea-acanthocytosis and McLeod syndrome, both with progressive basal ganglia and other multisystem features (see Chapter 19). Symptoms usually develop in adulthood but childhood onset is described. Some people with Huntington disease-like 2 or pantothenate kinase (PANK2) also have acanthocytes. In addition, acanthocytosis is associated with abetalipoproteinemia and hypobetalipoproteinemia, both of which can cause vitamin E deficiency (Jung et al. 2011; OMIM 200150 and 300842).

DISORDERS OF COAGULATION AND PLATELETS

Haemophilia carries a major risk of intracranial haemorrhage that may occur at any age. Haemorrhage may be extradural, subdural, subarachnoid or intraparenchymal. Haemorrhage can be spontaneous or triggered by trauma, including delivery, with the former more common in children with severe deficiency and the latter more prominent in milder forms. Presenting symptoms include headache and vomiting in
most cases, with or without focal features and behaviour change, although young children and neonates may only show drowsiness. Some children also develop spinal haematoma which present with back pain and which can lead to paraplegia. Neuroimaging indicates the extent and origin of the haemorrhage, which is best treated by medical means including clotting factor replacement whenever possible. Surgery, when indicated, should be deferred until the relevant clotting factor deficiency has been corrected. Deficiencies in other factors including V, VII, X and XIII, afibrinogenemia, and Von Willebrand disease, can also cause intracranial haemorrhage. Prophylactic replacement therapy may be indicated in severe deficiencies (Teranos Pinto et al. 1992; Quinones-Hinojosa et al. 2003; de Siboni et al. 2012; Labarque et al. 2013).

Acquired clotting factor deficiency due to vitamin K deficiency is discussed in the Liposoluble Vitamin Deficiencies section.

Severe thrombocytopenia, both genetic and acquired, and functional platelet defects such as Glanzmann thrombasthenia, can lead to intracranial haemorrhage (Fig. 27.6). Prenatal or neonatal alloimmune thrombocytopenia is due to maternal antibodies against platelet antigens, usually HPA1a. If not looked for by neonatal ultrasound, the prenatal onset form can present later in infancy with symptoms related to porencephalic cysts and an associated optic nerve hypoplasia whose mechanism is unexplained. Transfusions of compatible platelets, if necessary as an Intrauterine procedure; intravenous immunoglobulin administration to the mother prenatally and to the infant postnatally; and elective delivery by Caesarean section can all be useful protective measures. Monitoring of future pregnancies is also important as the risk persists (Davidson et al. 1989; Menell and Bussel 1994).

Thrombotic microangiopathies also cause thrombocytopenia together with other haematological features and multisystem involvement including the brain. Syndromes include thrombotic thrombocytopenic purpura (TTP), haemolytic-uraemic syndrome and some secondary forms associated with pregnancy, drugs, transplantation, malignancy and infection. TTP is caused by a deficiency of Von Willebrand factor (vWF), cleaving metalloprotease ADAMTS-13, which can be genetic or acquired. The former can manifest at any age including in neonates (Upshaw-Schulman syndrome). The acquired form, due to auto-antibodies to ADAMTS-13, is usually idiopathic but can be triggered by viral infections or drugs including beta-interferon, and is very rare in children. Neurological complications predominate, and include headache, seizures, focal deficits and varying degrees of encephalopathy (George and Nester 2014; Rosove 2014).

All forms of allogeneic transplantation can be associated with neurological complications, including acute and chronic encephalopathies of varying severity, seizures, focal deficits, movement disorders and ataxia, myelopathy, ototoxicity, neuropathies and myopathy. The causes are both procedure specific and generic. The latter include direct effects such as drug toxicity or radiation, or CNS infections secondary to immunosuppression.

Acute encephalopathy can be due to drug toxicity, acute demyelinating encephalomyelitis, PRES and hypertension, intracranial haemorrhage, hypoxic-ischaemic, metabolic and infectious causes, alone or in combination. Some of these can also present with focal signs.

Many chemotherapeutic and immunosuppressive agents can cause the adverse neurological effects listed above. The risks are agent, dose, route, age and pharmacogenetic related, and rare idiosyncratic responses are reported as well. Many neurotoxic effects are reported, more frequently in adults. A standardised terminology and grading system has been introduced by the National Cancer Institute (US Department of Health and Human Services 2010). Some specific effects reported in children are listed in Table 27.7.

Intracranial haemorrhage, including haemorrhagic infarction and subdural haematoma, can follow from thrombocytopenia secondary to bone marrow suppression.

Metabolic factors include renal and hepatic decompensation, which may be pre-existing as outlined in the Renal Disease and Hepatic Disease sections, acute electrolyte derangements, and those secondary to nutritional problems.
seizures with focal EEG changes including paroxysmal acute limbic encephalitis (PALE) with confusion, amnesia, latent infection. HHV6 can reactivate, especially if graft versus depletion may predispose to this complication. Diagnoses cytomegalovirus] predominate as causes of encephalitis. T-cell cella, human herpesvirus-6 (HHV6), Epstein–Barr (EBV) and infections also occur but do not usually cause encephalitis. Adenovirus infection also occurs but does not usually cause encephalitis. In the acute stage immediately post transplant, aspergillosis and toxoplasmosis are the most frequent causes of CNS infection. They are also important causes of focal lesions. Candida, which may originate from indwelling catheters, can also cause CNS infection. Bacterial infections are more often due to Gram-negative bacteria such as Pseudomonas aeruginosa, particularly after renal transplants, or enterococci, particularly after liver transplants, but staphylococcal infection can also occur. In solid organ transplants, acute infection can originate from the surgical procedure or the transplanted tissue. Since 2000, examples of the latter in adults have included rabies and lymphocytic choriomeningitis virus. Adenovirus infection also occurs but does not usually cause encephalitis.

In subsequent months, herpes viruses [herpes simplex, varicella, human herpesvirus-6 (HHV6), Epstein–Barr (EBV) and cytomegalovirus] predominate as causes of encephalitis. T-cell depletion may predispose to this complication. Diagnoses based on PCR of CSF cannot always distinguish active from latent infection. HHV6 can reactivate, especially if graft versus host disease (GvHD) develops, and manifests as posttransplant acute limbic encephalitis (PALE) with confusion, amnesia, seizures with focal EEG changes including paroxysmal later-alised epileptiform discharges (PLEDs), often hyponatraemia, and bilateral medial temporal lobe abnormalities on MRI. After several months, severe intractable seizures develop with regression in younger children or severe memory problems in older children. Herpes simplex virus encephalitis, which often does not have MRI changes, may have a better outcome than others. Varicella zoster virus encephalitis is rare, and occasionally can also have limbic features. More frequently VZV reactivation causes shingles followed by neuralgia and neuropathy. EBV infection, especially primary, is a major cause of post-transplant lymphoproliferative disorder, which can involve the brain. Rituximab can help in treatment. EBV can also cause a non-specific encephalitis. Progressive multifocal leucoencephalopathy due to reactivation of the JC (John Cunningham) polyomavirus is fortunately rare in children. Later bacterial infections include staphylococci and other Gram-positive or capsulated bacteria, especially pneumococcus; chronic graft versus host disease is a risk factor (Kawasaki et al. 1996; Hale et al. 1999; Koc et al. 2000; Doris et al. 2007; Schmidt-Hieber et al. 2011; Howell et al. 2012; Green and Michaels 2013; Styczynski et al. 2013; Tyler 2009a, b).

Acute or subacute encephalopathy therefore requires a detailed clinical assessment while investigations need to include neuroimaging, preferably MRI unless a child is too unwell to tolerate it, a full infection screen covering all possible agents, drug levels where appropriate, and a metabolic workup that includes electrolytes, measures of renal and hepatic function, glucose, ammonia and pH. Broad spectrum treatment is usually started before all results are available.

Seizures, as well as being a manifestation of an acute encephalopathy, can also occur in isolation due to drugs, metabolic abnormalities or focal insults. Investigations and management are similar to those above. However, it is also important to keep in mind that some anticonvulsants accelerate the catabolism of steroids, resulting in possible reduction of allograft survival. Treatment of seizures should be with non-enzyme-inducing drugs.

Strokes and stroke-like episodes can be vascular, due to causes such as emboli from intravascular catheters or haemorrhage due to thrombocytopenia, focal infections, or drugs. Asparaginase in particular inactivates anti-thrombin III and is associated with venous thrombosis. Acute demyelinating encephalomyelitis (ADEM) can present in a similar way. Neuroimaging also occasionally detects subdural collections (Coplin et al. 2001; Chen et al. 2012).

Movement disorders are not usually a major problems either in terms of frequency or severity. The main association is with tremor and rarely parkinsonian features in patients on long-term cyclosporine therapy. Acute myelopathy is mostly frequently caused by acute cord compression from intraspinal haematoma, due to haemorrhagic diathesis. If decompressed promptly, function can be preserved but often the long-term outcome is poor. Otherwise chronic myelopathy can be a late effect of radiotherapy to the spinal cord. Management should cover motor, sensory and sphincter complications.

![Table 27.7 Neurotoxic effects of chemotherapeutic and immunosuppressive agents in children](image)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Neurological adverse effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine/Thiotepa</td>
<td>Encephalopathy, seizures, axia</td>
<td>Gilman et al. (2011)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Insomnia, behavioural effects, myopathy, hypertension</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Seizures, PRES, intracranial haemorrhage, psychosis, tremor, hearing loss, myalgia, neuropathy</td>
<td>Bechstein (2000)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Fluictuant: hemiparesis, often alternating: dysphasia, confusion, headache, choreoathetosis, seizures; leukoencephalopathy with restricted diffusion in deep white matter on DWI</td>
<td>Inaba et al. (2008)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Seizures, PRES, intra-cranial haemorrhage, psychosis, tremor, hearing loss, myalgia, neuropathy</td>
<td></td>
</tr>
</tbody>
</table>

PRES, posterior reversible encephalopathy syndrome; DWI, diffusion weighted imaging.

Immunosuppression post transplant, or due to other causes, increases the risk of meningitis, encephalitis or focal infection by a variety of viral, bacterial, fungal and parasitic agents, both endemic and opportunistic. Symptoms include encephalopathy, fever, seizures, and focal features.

In the acute stage immediately post transplant, aspergillosis and toxoplasmosis are the most frequent causes of CNS infection. They are also important causes of focal lesions. Candida, which may originate from indwelling catheters, can also cause CNS infection. Bacterial infections are more often due to Gram-negative bacteria such as Pseudomonas aeruginosa, particularly after renal transplants, or enterococci, particularly after liver transplants, but staphylococcal infection can also occur. In solid organ transplants, acute infection can originate from the surgical procedure or the transplanted tissue. Since 2000, examples of the latter in adults have included rabies and lymphocytic choriomeningitis virus. Adenovirus infection also occurs but does not usually cause encephalitis.

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Neuropathies can either be focal; for example, ophthalmoplegic, ototoxic or femoral post catheterisation, plexopathies, or peripheral polynuropathies, following drug therapy (see Table 27.7). Vinca alkaloids usually cause an asymptomatic neuropathy, but if they are given to a patient with a pre-existing hereditary neuropathy, such as CMT1A, severe weakness can result, with a prolonged recovery time (Chauvenet et al. 2003).

Myopathy mostly follows steroid use, which may be long term. Myalgia can occur with some chemotherapeutic agents (see Table 27.7).

Chronic encephalopathy can manifest as non-progressive learning difficulties, either global or specific, reflected in reduced IQ levels and disorders of executive and memory functions, and behaviour problems. Both radiation and chemotherapy are well-recognised contributors. Survivors of acute encephalopathies are also at increased risk.

Late effects of focal insults can also lead to central motor disorders such as hemiparesis, epilepsy, global or specific intellectual deficits and behaviour problems.

### HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Haematopoietic stem cell transplants are derived from bone marrow or blood, including cord blood, and can be autologous or more usually allogeneic, from a matched donor. They can be used in the treatment of malignancies such as leukaemia and lymphoma, severe haemoglobinopathies, immune deficiencies, neurodegenerative disorders such as adrenoleukodystrophy and have been tried in some metabolic conditions. All involve high-dose chemotherapy while the treatment of malignancy may include intrathecal chemotherapy and craniospinal radiotherapy which carry their own specific risks.

Older case series reported neurological complications during and after bone marrow transplantation in children of up to 40% or more, but more recent series report approximately 16%. Associated mortality rates are up to 30%. Certain causes predominate at different stages of the transplantation process. Weber et al. (2008) divided these into two groups. The first had transient self-limiting symptoms often seizures or encephalopathy during conditioning, lasting less than 24 hours, with normal neuroimaging: some had idiopathic intracranial hypertension. The second had progressive symptoms and abnormal neuroimaging. The latter could be further divided into early, less than 100 days (CNS bleeds, aspergillosis, toxoplasmosis, or drug toxicity); middle, less than 6 months (drug toxicity); and late, over 6 months (viral infection or CNS relapse) (Faraci et al. 2002; Iguchi et al. 1999; Uckan et al. 2005).

The main condition-specific problem is graft versus host disease (GvHD) in allogeneic transplants. It can be difficult to find the balance between tolerable toxicity from the agents used, and the increased risk of GvHD if lower dose regimens are followed. As well as the generic neurological complications summarised above, procedure-specific complications include intracranial haemorrhage due to bone marrow suppression and neurological complications of GvHD. In one series, 11% of patients developed neurological complications due to intracranial haemorrhage, mainly subdural and secondary to thrombocytopenia, metabolic encephalopathy or infection. Other series report important drug side effects; for example, from cyclosporine. Stroke is usually haemorrhagic, either due to thrombocytopenia or fungal infection. Polymyositis is reported in association with other features of GvHD syndrome (Iguchi et al. 1999; Coplin et al. 2001; Faraci et al. 2002; Uckan et al. 2005; Klein et al. 2007).

The longer term neurocognitive effects are unclear as 5-year follow-up studies give contradictory results, partly due to differing inclusion criteria, but unrelated donor transplantation, total body irradiation and GvHD appear to increase the risk of adverse outcomes. The effect of socio-economic status is also very significant (Boulad et al. 1998; Phipps et al. 2008; Shah et al. 2008; Lin et al. 2009).

### HEART AND HEART LUNG TRANSPLANTATION

Complications of cardiac transplantation include those related to severe cardiac failure pre- and posttransplant, which may require ventricular support devices, cardiopulmonary bypass surgery and immunosuppressant therapy. In heart transplantation, the main procedure-specific risk is hypoxic-ischaemic encephalopathy. Some of the underlying cardiac conditions have additional background associations as discussed in the Cardiac Disorders section. Although good results are now obtained, the neurodevelopmental outcome remains a concern (Wray and Radley-Smith 2006; Chinnock et al. 2008).

### LIVER TRANSPLANTATION AND INTESTINAL TRANSPLANT

Liver transplantation is a powerful treatment for acute and chronic hepatic failure and has achieved considerable success. It should be performed before there is evidence of cerebral oedema as the results are otherwise poorer. However, transplantation and the immunological abnormalities that its treatment implies may give rise to neurological complications. One series reported early (<3 months after transplant) complications in 14% and later ones in 17%. Seizures predominated in both groups, followed by encephalopathy and headache. Longer term neurocognitive outcomes are reduced compared to control groups, especially in younger age groups, although this could have several mechanisms.

Intestinal transplantation can be performed with or without multivisceral (liver etc.) transplantation. The longer term outcome in survivors remains poor, with 74–96% of those receiving multivisceral transplant before the age of 3 years showing cognitive problems in one series (Stewart...

**KIDNEY TRANSPLANTATION**

Rejection encephalopathy is discussed in the Renal Diseases section. Otherwise, the generic risks are the main causes of acute neurological problems. Longer term results show reductions in neurocognitive function and are influenced by the underlying cause, neurological complications, age at transplant and delay before transplant (Falger et al. 2008; Johnson and Warady 2013; Moser et al. 2013).

Symptomatic hypoglycaemia has been observed months to years following renal transplantation (Wells et al. 1988). It occurred in children receiving propranolol and responded to discontinuation of the drug.

**REFERENCES**


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Neurodevelopmental Disabilities and their Management

Bruce K Shapiro

Development is a series of processes by which mature function is achieved. At birth, humans are relatively immature and most organ systems do not function in a mature fashion. The processes that guide development are complex and incompletely understood.

Neurodevelopment is also not random. It is ordered, predictable and measurable, for example, most children roll before they sit, and sit before they crawl, and crawl before they walk. The achievement of the skills, or milestones, is the functional expression of the underlying maturational processes. Neurodevelopment reflects the integrity of the child’s nervous system. Most systems of assessment focus on the achievement of new skills or milestones, but neurodevelopment is not unidirectional. Although the most dramatic changes are in the appearance of new functions, previously achieved functions may be performed more efficiently, and some functions regress.

Perturbations of the developmental process may result from many different aetiologies. Genetic, metabolic, infectious, traumatic, hypoxic–ischaemic, immunological and toxic are some of the factors that disrupt the developmental process. These factors affect multiple areas of the brain and result in diffuse brain dysfunction. As a consequence, dysfunction in one area of development projects dysfunction into other areas of development, for example, children with motor delays frequently have disordered language development. Attention-deficit–hyperactivity disorder (ADHD) co-occurs with disorders of written expression. Furthermore, the most common reason for failure of a treatment programme is missing an important co-occurring disorder (Kube and Shapiro 1996).

Developmental dysfunction is longitudinal. The abnormality that results from the insult may cause immediate dysfunction but also affects the ongoing maturational processes, later dysfunction may be noted. For example, a child who evidences delay in achievement of walking may ultimately walk but later show abnormality in his language function or difficulties with executive function and academic learning.

PRESENTATIONS OF NEURODEVELOPMENTAL DISABILITIES

Early identification of developmental disorders has the following four important functions: (1) it enables the early provision of services, (2) it allows for long-term planning, (3) it enables families to adapt to the child's dysfunction and (4) it enables investigation for aetiologies and consideration of the genetic implications for the family. Techniques for the early identification of neurodevelopmental disabilities are screening, risk registries and parental referral (Shapiro 2011).

Screening is the application of a technique to an asymptomatic population. Ideally, screening is done before the child becomes symptomatic; the tools used have good classification abilities and there are effective interventions for the condition. The outcome of screening is risk, not diagnosis. Positive screening tests require confirmatory assessments to establish a diagnosis.

Perhaps the most effective screening is that of newborn infants. Currently, most states in the USA screen for 29 conditions, but the capability, in part related to refinements to tandem mass spectrometry techniques [e.g. matrix-assisted laser desorption/ionisation (MALDI)–time of flight (TOF)], exists for identifying over 50 conditions (Table 28.1). The impact of this approach for children with phenylketonuria or congenital hypothyroidism has been dramatic. The impact of universal screening of newborn infants for hearing impairment has been less than metabolic screening because of the low rate of follow-up confirmatory testing; 35.3% of US infants who failed the initial screening were lost to follow-up (Centers for Disease Control 2011). The impact of the programme is greater in countries where the rate of complete evaluations is higher (see Chapter 23). Screening for neurodevelopmental disabilities is less effective because of the psychometric properties of the tools.

Risk registries are established to target certain populations for surveillance, based on their belonging to a group. Risk registries based on historical risk are not effective because most children do not have the condition that they are at risk of having and most with the condition do not come from a risk group, for example, children who are born preterm have higher rates of cerebral palsy (CP), as much as ten times the rate in the general population. However, given the rarity of CP (approximately two in 1000), almost all children who are born preterm do not have CP (approximately 94% in infants with birthweights <1500g; Oskoui et al. 2013). Most children with CP come from the population not born preterm.
On the other hand, risk based on performance is a useful method for identifying children who may need intervention, for example, 5-year-old children with persisting language delays are at extremely high risk of evidencing academic underachievement (Snowling and Hulme 2012).

Most child neurologists with an interest in neurodevelopment are not involved with the early identification of children with neurodevelopmental disorders. More often, they are asked to evaluate children who have failed to meet age-appropriate expectations or whose development has been in question as part of an acute neurological presentation (Table 28.2). The following are the roles of the consultant: (1) establish a diagnosis, (2) delineate co-occurring disorders, (3) determine aetiology, (4) treat and (5) participate in the establishment of a management programme.

### Table 28.1 Conditions potentially included in screening of newborn infants

#### CORE CONDITIONS

**Hearing**
- Congenital deafness
- Congenital deafness

**Endocrine**
- Congenital hypothyroidism
- Congenital adrenal hyperplasia

**Haemoglobinopathies**
- Sickle cell anaemia
- HbS β-thalassaemia
- Sickle cell disease

**Metabolic**
- Fatty acid disorders
  - Carnitine transporter defect
  - Long-chain 1-3-hydroxyacyl-CoA dehydrogenase
  - Medium-chain acyl-CoA dehydrogenase
  - Trifunctional protein deficiency
  - Very-long-chain acyl-CoA dehydrogenase
- Organic acid disorders
  - Glutaric aciduria type I
  - 3-Hydroxy 3-methylglutaric aciduria
  - Isovaleric acidemia
  - 3-Methylcrotonyl-CoA carboxylase
  - Methylmalonic acidemia (vitamin B12 disorders and methylmalonyl-CoA mutase)
  - β-Ketothiolase
  - Propionic acidemia
  - Multiple carboxylase
- Amino acid disorders
  - Arginosuccinate aciduria
  - Citrullinaemia type I
  - Homocystinuria
  - Maple syrup urine disease
  - Phenylketonuria/hyperphenylalaninaemia
  - Tyrosinaemia type I

**Other**
- Biotinidase
- Galactosaemia (transferase deficiency)
- Cystic fibrosis

**Additional disorders that may be included in screening panel**
- Critical congenital heart disease
- Severe combined immunodeficiency
- 5-Oxypyrrolinuria
- Glucose-6-phosphate dehydrogenase
- Non-ketotic hyperglycaemia
- Carbamoyl phosphate synthetase
- Hyperammonaemia/orithinaemia/citrullinaemia (ornithine transporter defect)
- Prolianaemia
- Ethylmalonic encephalopathy
- Human immunodeficiency virus
- Toxoplasmosis
- Pompe, Krabbe, Niemann–Pick, Gaucher and Fabry diseases, mucopolysaccharidosis (MPS) type I, MPSII

#### SECONDARY TARGET CONDITIONS

(either required by law or likely to be detected and reported by multiple reaction monitoring screening)
- Fatty acid disorders
  - Carnitine acylcarnitine translocase
  - Carnitine palmitoyltransferase I
  - Carnitine palmitoyltransferase II
  - Dienoyl-CoA reductase
  - Glutaric acidemia type II
  - Medium-/short-chain 1-3-hydroxyacyl-CoA dehydrogenase
  - Medium-chain ketoyl-CoA thiolase
  - Short-chain acyl-CoA dehydrogenase
- Organic acid disorders
  - 2-Methyl-3-hydroxybutyric aciduria
  - 2-Methylbutyryl-CoA dehydrogenase
  - 3-Methylglutaconic aciduria
  - Methylmalonic aciduria (Cbl C, D)
  - Isobutyryl-CoA dehydrogenase
  - Malonic acidemia (malonyl-CoA decarboxylase)
- Amino acid disorders
  - Arginaemia (arginase deficiency)
  - Defectors of biopterin cofactor biosynthesis
  - Defects of biopterin cofactor regeneration
  - Citrullinaemia type II
  - Benign hyperphenylalaninaemia
  - Hypermethioninaemia
  - Tyrosinaemia type II
  - Tyrosinaemia type III
- Other metabolic disorders
  - Galactose epimerase
  - Galactokinase

National Newborn Screening and Global Resource Center (2013).

#### QUANTIFYING DEVELOPMENT

Developmental assessment stems from the empirical observation that children follow the same developmental course and what varies is the age of achievement. As a consequence, a child’s development can be described by a function versus time plot which compares the age that a child achieves a milestone with the age at which that milestone is usually achieved (Fig. 28.1). As most children start at zero, the rate can be reduced to...
a ratio or developmental quotient which compares the age of achievement of a milestone with the chronological age.

The longitudinal collection of developmental achievements enables primary care providers with a method of charting the child’s development and defining several patterns of abnormality that may lead to early diagnosis. Four longitudinal patterns of development may be defined. The most common is seen in typical children and that is a pattern of a stable rate – 1 year olds doing 1-year-old activities, 2 year olds, 2-year-old activities, and so on.

A second pattern is seen when an acute event intervenes in the developmental processes. This may be noted in children who have suffered traumatic brain injury, brain infection or toxic exposures. The third pattern is noted in children who are proceeding at a developmental rate and then accelerate their rate of development. This pattern may be seen in infants who were born preterm and show acceleration of their development after achieving physiological stability or in children who are recovering from acute events.

A fourth pattern is associated with plateau/regression. This pattern may be evidenced in one or two areas of development, as might be seen in the language regression noted in the Landau–Kleffner syndrome or autistic spectrum disorder. It may represent a slowing of developmental progress that is not associated with loss of skills, as might be seen in children who are diagnosed as having mixed receptive–expressive language disorders in preschool, but fail to progress and are considered intellectually limited by middle school. Finally, this pattern is seen in children who show generalised plateauing and regression, as might be observed in neurodegenerative disorders.

When used in a cross-sectional fashion, the relationship between function and age allows for the following three conditions to exist: delay, asynchronous development or dissociation, and non-sequential development or deviance.

Delay brings children to attention. It has different definitions – developmental quotients of 85%, 75% and 70% – have all been recommended and are used in different situations. Although there is significant variability in developmental achievements within the typical population, children whose development is significantly slowed are remarkably consistent in their developmental quotients.

Dissociation facilitates early diagnosis. In the typical child, all developmental areas progress at a similar pace. Asynchrony in development is defined as a 15% difference in developmental quotients. By comparing developmental quotients, early diagnosis is possible and is illustrated in Table 28.3.

Non-sequential development or deviance occurs when the developmental progression is violated. Such examples occur in the case of bottom shuffling, where children bypass crawling or, in the case of language development, they have many words but are not using phrases or sentences. Non-sequential development may be seen in children with autistic spectrum disorders, but also in children with mixed receptive–expressive language disorders or who are being ‘over-programmed’. Non-sequential development is not a normal variant and requires additional exploration.

### NEURODEVELOPMENTAL DISORDERS

‘Neurodevelopmental disorders’ is a term used to describe a group of brain-based disorders that have their onset during childhood and result in substantial functional limitations.
Part XII  Developmental and Neuropsychiatric Disorders of Childhood

These disorders may result from a large number of causes. The neurodevelopmental disorders are defined functionally and do not specify severity, other than to impair function, mechanism or prognosis (Table 28.4).

As a consequence, these diagnoses are thought to be dimensional rather than categorical. The boundaries of these disorders are often indistinct, for example, at what point does clumsiness become CP? How much social impairment is required to establish the diagnosis of autism?

Frequently, a child may have multiple co-occurring neurodevelopmental disorders. Children with language disorders often have abnormalities of tone and coordination. Approximately 50% of children with CP have intellectual disability. A third of children with autism meet criteria for ADHD. The prevalence of co-occurring disorders is determined, in part, by the depth of the evaluation. Whether this represents comorbidity or multiple expressions of a common aetiology is a subject of debate.

One reason for the high rate of co-occurring conditions is that the aetiologies of neurodevelopmental disorders result in diffuse brain injury, with consequent functional impairment in multiple areas. Trauma, infection, toxins, hypoxia–ischaemia, immunological, genetic, metabolic, malformations, endocrine, nutritional and oncological aetiologies have been associated with neurodevelopmental disorders. The clinical implications of this finding are twofold as follows: developmental dysfunction in one area of development should warrant exploration of other areas of development and re-evaluation is indicated if a treatment programme is not working.

Infancy

Gross motor development is the major developmental focus between age 6 and 18 months. Most referrals are made around a year of age, but evidence of motor dysfunction is apparent before that time and new diagnoses of CP should be made by 18 months in most cases.

The motor quotient was a tool developed to predict whether children who are motor delayed at 8–18 months will walk by age 2 years. This measure compares the age of motor achievement and chronological age. Children who have a motor quotient of <50% are at high risk for significant motor delays (Capute and Shapiro 1985). Children who have motor quotients between 50% and 75% often have other developmental disabilities.

Further evaluation of motor function will evaluate whether the child has persistence of functions that are suppressed by brain maturation, delayed appearance of functions that are closely linked to volitional motor function and classic neurological findings. Primitive reflexes are brainstem-mediated responses that appear late in gestation.

Table 28.4  Neurodevelopmental disabilities: definitions and prevalence

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic spectrum disorders (1.2%)</td>
<td></td>
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<tr>
<td>These disorders are characterised by (1) a qualitative impairment in reciprocal social interaction and (2) restricted, repetitive and stereotyped patterns of behaviour, interests and activities</td>
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<tr>
<td>Attention-deficit–hyperactivity disorder (11%)</td>
<td></td>
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<tr>
<td>ADHD is characterised by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity, which has persisted for more than 6 months and had its onset before age 12</td>
<td></td>
</tr>
<tr>
<td>Blindness (3 in 10 000)</td>
<td></td>
</tr>
<tr>
<td>Visual acuity (vision) of ≤20/200 (6/60) in the better eye with best correction possible, or a visual field of &lt;20°</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy (0.2–0.4%)</td>
<td></td>
</tr>
<tr>
<td>CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems</td>
<td></td>
</tr>
<tr>
<td>Deafness (0.1%)</td>
<td></td>
</tr>
<tr>
<td>An inability to hear: severe deafness is 71–90dB hearing loss; profound is &gt;91dB</td>
<td></td>
</tr>
<tr>
<td>Intellectual disability (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Significant limitations in both intellectual functioning and adaptive behaviour, which cover many everyday social and practical skills, and originate before the age of 18</td>
<td></td>
</tr>
<tr>
<td>Mixed receptive–expressive language disorder (RELD, 4–6%)</td>
<td></td>
</tr>
<tr>
<td>RELD is one of the specific developmental disorders characterised by weakness in language functions, but is distinguished from intellectual disability by relative sparing of non-language skills</td>
<td></td>
</tr>
<tr>
<td>Specific learning disabilities (5–7%)</td>
<td></td>
</tr>
<tr>
<td>Specific learning disabilities make up a group of disorders that manifest as academic underachievement despite having adequate academic instruction, and are not due to intellectual disability</td>
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</tbody>
</table>
and are no longer evident by the latter part of the first year. Persistence of obligatory or excessive primitive reflexes is associated with CP. Postural responses maintain the head perpendicular to the floor and are intimately linked to volitional motor activity. The classic neurological examination evaluates strength, tone (after modifications for gestational age) and symmetry. The algorithm (Fig. 28.2) demonstrates how the use of volitional motor activity, postural responses and primitive reflexes can be combined to come to the early diagnosis of CP (Shapiro and Gwynn 2008).

**Toddlers**

Language acquisition is the major task of toddlers. Vocabularial size enlarges exponentially from 12 to 36 months and is a major focus of assessment. During this period vocabulary increases from a single word at a year to ten words at 18 months, 50 words and sentences at 2 years to 350 or more words, plurals and pronouns at age 3. In addition to vocabulary size, toddlers can follow commands, identify body parts and point to pictures and name them. Stranger anxiety may limit the ability of toddlers to participate in evaluations and so much of the evaluation may have to be done by interviewing parents. Fortunately, parents are reliable reporters of their children's current function. Vocabulary size estimates may be inflated because of echolalia, proper names, programmed speech or single word phrases (e.g. 'thank you', 'stop that' or 'my, what a beautiful day it is outside'). Words must be used routinely to count as vocabulary size, sentences must have novel constructions and development must be coupled. Uncoupling of language development is a form of deviance. Be wary of the child who has more than 50 words but is not using sentences or the child who uses only nouns.

**Preschool**

Preschool is a time of major developmental change. It is associated with increasing independence and socialisation. Major foci include socialisation, play, attention and activity, behavioural regulation and mastery of pre-academic skills. Fine motor demands are reflected in dressing, colouring, cutting, pasting, and pencil-and-paper tasks. The gross motor and vocabulary skills of early epochs should be integrated. Preschoolers often change their developmental trajectory and, with maturation, grow into or out of diagnoses. The large amount of behaviour to be sampled usually requires the services of a psychologist or speech language pathologist. The most common diagnoses made in the preschool period are related to language function and include the following: mixed receptive–expressive language disorder or autistic spectrum disorder. Severe intellectual disability is usually manifest before the preschool period. Global developmental delay, operationally defined as significant delay in two or more developmental domains (motor, speech-and-language, social or daily activities; Ashwal et al. 2003), may be used for children with milder intellectual disability to provide time for clarification of the diagnosis. Although ADHD may be manifest during this time the diagnosis may be deferred until the start of school.

**School-Aged Dysfunction**

The presentation of developmental dysfunction in school-aged children is not random (Lewis et al. 2013). Most often children are referred for not meeting age-related expectations. Table 28.5 lists typical school expectations. School-aged children with neurodevelopmental dysfunction often have behavioural disturbance. ADHD frequently accompanies disorders that cause school underachievement, and adjustment disorders with anxiety or mood issues are common. Some children would rather be thought bad than

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**Table 28.5 School expectations**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Expectation/area of focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preschool</td>
<td>Play</td>
</tr>
<tr>
<td>(age 30 months to 4 years)</td>
<td>Behaviour</td>
</tr>
<tr>
<td></td>
<td>Colouring, cutting, pasting</td>
</tr>
<tr>
<td>Early primary</td>
<td>Fundamental reading (decoding)</td>
</tr>
<tr>
<td>(age 5–8 years)</td>
<td>Regrouping</td>
</tr>
<tr>
<td>Later primary</td>
<td>Reading for information</td>
</tr>
<tr>
<td>(age 9–11 years)</td>
<td>Written expression</td>
</tr>
<tr>
<td>Middle school</td>
<td>Chapter reading</td>
</tr>
<tr>
<td>(age 12–14 years)</td>
<td>Organisation</td>
</tr>
<tr>
<td></td>
<td>Long-term assignments</td>
</tr>
<tr>
<td>High school</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Defeat</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Disease (e.g. thyroid)</td>
</tr>
</tbody>
</table>

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**Figure 28.2 Algorithm for early diagnosis of cerebral palsy.** (Modified from Shapiro and Gwynn 2008.)
unable and act out in the classroom or at home. Young children may be called oppositional defiant when they are protesting about things that they cannot do. Often practitioners confront a dilemma such as the following: if he behaved better he would learn more versus if he was in a situation that was more consonant with his educational needs he would behave better.

Early primary school (age 5–8 years) is when most referrals are made for evaluation of dyslexia or ADHD. The major objective of early primary school is the mastery of fundamental reading. Fundamental reading, or decoding, requires the attachment of sounds to symbols and derivation of meaning from the words. Interruption of these processes may result from fundamental inability to attach sounds to symbols (dyslexia), a more generalised language disorder, intellectual limitation or problems with sequencing. Behaviour, particularly activity and attention, is also an area of focus.

Later in primary school (age 8–11 years), the focus shifts from learning to read to reading to learn. Reading for comprehension, inference, expository writing (themes) and mastery of the primary mathematical processes (adding, subtracting, multiplying and dividing) are the main areas of focus. Just as reading is a complex function, mathematics builds on attention/working memory, sequencing and reading (word problems), as well as numeracy.

Middle school (age 11–14) stresses organisational skills and independent function. By middle school the basic processes have been mastered and the focus shifts to process. Children are responsible for following schedules, planning long-term assignments and turning in homework when it is due. The nature of the work also changes. Chapter reading predominates and the child has to do more than read all the words; he has to integrate the material and extract meaning. Notes must be taken. The thinking required is more than recall. Against this backdrop are the social challenges that confront adolescents.

When children present for the first time in high school they are not presenting with issues relating to the content of the curriculum. For children who have no previous history of academic difficulty, consideration should be given to other conditions such as thyroid dysfunction, psychiatric disorders (e.g. depression) or substance abuse. Some children who have a history of mild academic underachievement give up. Some are very bright and have been using their intellect to cover their inefficiencies. Others may be using extracurricular activities to provide the boost that enables them to persevere. Supportive counselling, focusing on areas of strength, and classroom accommodations are effective interventions.

AGE AND MATURATIONAL EFFECTS

Some children who have been diagnosed with neurodevelopmental disorders may grow out of the diagnosis whereas others grow into it, and still others change their diagnoses. Some children with global developmental delay may have evidence of typical development at an older age. Between 3% and 25% of children who have been diagnosed as being on the autism spectrum do not maintain that diagnosis (Helt et al. 2008). Hyperactivity is infrequently seen after adolescence.

This phenomenon is also seen in motor domains, for example, a child may present with motor delay and signs of CP in infancy, but lose that diagnosis by early childhood. It is common to see contractures develop or progress with age in children with CP.

Finally, maturation and ageing may affect the diagnosis of dysmorphic syndromes, for example, children with Prader–Willi syndrome may present as failure to thrive. Children with fetal alcohol syndrome are more easily diagnosed as toddlers than as adolescents.

Early dysfunction that does not result in disability may serve as a marker for later developmental dysfunction, for example, an infant who presents with motor delay may close the gap as a toddler but later have evidence of language and academic dysfunction. Early mixed receptive–expressive language disorder may be a harbinger of later intellectual disability in early adolescence.

The reasons why some children change their diagnoses as they age are not clear. Damage to the developing brain not only has immediate effects but may also confer secondary effects from the response to the initial trauma (Fathali et al. 2011). Trauma at an earlier point in development may affect subsequent function. These longer-term effects may not be evident until the demands of the situation exceed the child’s abilities. ADHD is typically not diagnosed until children are in group settings, where conforming to a set of rules is required. Dyslexia and other specific learning disabilities are not diagnosed until the child is exposed to formal academic studies, even though the neural substrate for these disorders is present. Intellectual disability may not be fully manifested until the failure to achieve formal operations can be documented. Compensatory mechanisms may ameliorate the dysfunction through alternative means, children who were born preterm and have globally normal language development show atypical functional magnetic resonance imaging (MRI) connectivity on language tasks (Mullen et al. 2011).

AETIOLOGICAL EVALUATIONS

Neurodevelopmental disorders may result from a wide range of disorders. Establishing the diagnosis is unique to the discipline of medicine. Knowledge of the aetiology of the neurodevelopmental disorder often relieves parental guilt by reinforcing that the disability could not be avoided by changing their behaviour. Aetiological diagnosis improves our prognostic ability, guides the search for associated dysfunctions and enables the risk for a subsequent pregnancy to yield a child with the same diagnosis. Finally, an aetiological diagnosis provides insight into the biological mechanism of the disordered function and the potential for targeted pharmacotherapy of neurodevelopmental disorders.
Embarking upon a search for the aetiology should be undertaken in a considered fashion. Among the questions to answer are the following: ‘What are the parents’ wishes?’ For some parents the aetiology is not an issue whereas for others it is the major issue. ‘Does the history or physical examination provide clues to a diagnostic pathway?’ ‘What is the type and nature of the developmental disability?’ Evaluations of children with language disabilities are usually unrevealing although evaluations of children with motor impairment, cognitive dysfunction, microcephaly and epilepsy are. Clinical practice guidelines that are based on literature reviews have been developed by professional societies to aid the diagnostic search. The American Academy of Neurology has protocols for global developmental delay (Shevell et al. 2003; Michelson et al. 2011), autism (Filipek et al. 2000) and CP (Ashwal et al. 2004). The American Academy of Pediatrics has protocols for global developmental delay (Moeschler and Shevell 2006), ADHD (Wolraich et al. 2011), autism (Johnson and Myers 2007) and a recent protocol for children with motor delay (Norton and Murphy 2013). The American College of Genetics has clinical guidelines for global developmental delay (Curry et al. 1997). Each practice guideline was developed for a specific diagnosis and based on existing literature, but the guidelines were not established as a ‘cookbook’. They were meant to be modified, based on the clinical condition.

A review of the clinical practice guidelines reveals commonalities that span the spectrum of developmental dysfunction. A comprehensive history and physical examination are the first step in the aetiological investigation. Neuroimaging and genetic studies are also recommended. Additional consultations and studies must be guided by the initial evaluations.

The history and the physical examination are the foundation of the aetiological evaluation. There is an almost endless list of conditions that lead to neurodevelopmental disability, and the number of evaluations that can be performed is almost as large. Aimless evaluation that is not directed by the clinical state results in many unneeded tests and runs the risk of not uncovering a known aetiology. All of the clinical guidelines recognise the importance of the clinical evaluation as the guide to further evaluation.

The purpose of the history is to develop a differential diagnosis. To that end the history must answer several questions. What is the presenting complaint? Often this is confounded by a listing of professionals who have interacted previously with the child and a longer list of the diagnoses that they have applied. As noted above, multiple coexisting disorders are common. However, to develop an effective management programme, it is critical to establish what the most troublesome problem is.

The history should document the child’s current functions for the following: language, motor, social, dressing, feeding, toileting and academic. Is the presenting symptom limited to a single area of development such as language or motor systems, or is it part of a more generalised process, as might be the case in intellectual disability?

Is the course of this process one of slow progress, abrupt onset with a reset of the developmental trajectory, episodic or regressive? Most of the neurodevelopmental disorders follow a course of slow progress. Disorders with an abrupt onset may suggest psychiatric, infectious, trauma or immunological disorders. Episodic disorders suggest epilepsy or genetic/metabolic processes.

Regression is an ominous sign, and may be seen as the end-result of many progressive disorders. Neurometabolic, neurodegenerative, endocrine and immunological disorders, toxins and epilepsy have all been associated with regression in multiple developmental areas. The regression seen in autism is limited to language and concomitant social areas, and does not affect motor function. At the early stages regression may be hard to appreciate and serial evaluations are warranted. Declining performance on standardised tests may be a failure to maintain the developmental trajectory and not a true regression.

The severity of the impairment is established by a quantitative approach to development. Obtaining a history of developmental achievements provides the basis for this approach in young children (see Table 28.6 for selected milestones). Parents are excellent historians if the clinician is precise in his or her questioning. If a parent has difficulty establishing an age of achievement for a specific task, the clinician may look to important life events, for example, ‘Was she walking at her first birthday?’ and ‘What was he saying last Christmas?’. Parents are reliable in the reporting, especially in the face of delay. The developmental quotient derived from a parental estimate of functional age often corresponds to the results of formal testing in young children.

The reliability of developmental history may be augmented through the use of developmental milestones, in a longitudinal fashion, to develop trajectories which decreases the importance of single milestones. Reviewing baby books, photos, video recordings, and previous evaluations, screenings and school reports provides almost concurrent evidence of developmental achievements.

Threats to the validity of a milestone approach include physiological instability, using the wrong milestones, misinterpreting responses and crediting behaviour that is emerging. Developmental assessment of children who are physiologically suboptimal may underestimate the child’s true ability and has limited prognostic ability. Evaluating a child who is physiologically unstable may be a useful measure of current function and may provide a basis for short-term interventions. For these children, serial assessments should be undertaken until physiological stability has been achieved and a valid evaluation achieved.

To be clinically useful a milestone must frequently occur in the target population, be clearly observed, occur within a narrow time frame and have prognostic significance. Using the wrong milestones is another threat to the validity of the developmental assessment. There are milestones assigned to many functions, but most have limited utility in defining developmental trajectories, for example, a milestone of when
an infant starts to hold the bottle is not particularly useful in a population where breastfeeding is the norm. Using forks and spoons is not the norm in certain cultures. Greeting a familiar person is difficult to interpret and is not clearly observed. Is simple curiosity about who is at the door credited? Does the milestone require the child to say, ‘Hi!’ or start a conversation? How does it differ from absence of stranger anxiety? A milestone that normally occurs between 24 and 36 months, as in toilet training, has limited utility if you are evaluating a preschool child. Finally, there are milestones that occur in most children within narrow age norms and are easily observed, but do not have strong prognostic value, for example, drawing a circle in a clockwise or anticlockwise fashion.

Misinterpreting responses is another source of error in developmental assessment. It may result from giving credit to emerging behaviours, which tends to overestimate the child’s ability. To truly credit a skill requires the skill to be firmly established. Another error, in the language area, is misinterpreting responses. Echolalia, single word phrases (e.g. stop that, thank you) and programmed speech (e.g. language that is learned from the television and used as filler) are examples of language behaviours that result in inflated estimates of function. To minimise these effects requires that the child use words spontaneously, appropriately and with novel constructions.

The history should also investigate symptoms of neurological dysfunction. Vision and hearing status should be queried. Previous or current alterations in consciousness, e.g. loss of consciousness from trauma or associated with seizures or staring spells, should be noted. Behaviours relating to maintenance of state, feeding, sleeping and elimination should be noted. Age-appropriate social interactions and peer acceptance are important markers of language function. Increased or decreased levels activity should be investigated. General medical symptoms should be reviewed relating to growth, exercise tolerance, and cardiopulmonary, gastrointestinal, musculoskeletal, genitourinary and integumentary systems.

Neurodevelopmentally significant events should be reviewed. A prenatal history of maternal chronic disease or thyroid dysfunction, fetal wastage, exposures (toxic or infectious), fetal movement quality, maternal weight gain/fetal growth, presentation and length of gestation have been related to suboptimal developmental outcomes. Natal factors that should be reviewed relate to the conduct of labour and delivery, the need for resuscitation, birthweight, intrauterine growth retardation, newborn infant seizures, intracranial haemorrhage, infection, respiratory support, pneumothorax, feeding difficulties, necrotising enterocolitis, movement abnormalities, hyperbilirubinaemia and autonomic dysfunction. Postnatal factors include hospitalisations, trauma, surgeries, toxic exposures (e.g. lead, mercury, cigarette smoke, bisphenol A), significant infections (e.g. meningitis, encephalitis), seizures and major organ system dysfunction. Previous evaluations should be obtained.

Family history should develop a three-generation pedigree that focuses on neurodevelopmental dysfunction. A family history of intellectual disability, autism, dyslexia, mixed

**Table 28.6  Selected developmental milestones**

<table>
<thead>
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<th>Age</th>
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<tr>
<td><strong>Gross motor</strong></td>
<td></td>
</tr>
<tr>
<td>Rolls (both directions)</td>
<td>5 months</td>
</tr>
<tr>
<td>Sits (alone)</td>
<td>6 months</td>
</tr>
<tr>
<td>Comes to sit</td>
<td>8 months</td>
</tr>
<tr>
<td>Crawls (locomotion in quadruped)</td>
<td>8 months</td>
</tr>
<tr>
<td>Cruises</td>
<td>9 months</td>
</tr>
<tr>
<td>Walks</td>
<td>12–15 months</td>
</tr>
<tr>
<td>Runs</td>
<td>15–18 months</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
</tr>
<tr>
<td>Smiles</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Coos</td>
<td>2 months</td>
</tr>
<tr>
<td>Babbles</td>
<td>6 months</td>
</tr>
<tr>
<td>Mamma/Dadda</td>
<td>11 months</td>
</tr>
<tr>
<td>First word</td>
<td>11 months</td>
</tr>
<tr>
<td>Four to six words</td>
<td>15 months</td>
</tr>
<tr>
<td>Seven to 20 words</td>
<td>18 months</td>
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<tr>
<td>Fifty words/two-word phrases</td>
<td>24 months</td>
</tr>
<tr>
<td><strong>Fine motor</strong></td>
<td></td>
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<tr>
<td>Hands open</td>
<td>3 months</td>
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<tr>
<td>Hands midline</td>
<td>4 months</td>
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<tr>
<td>Transfers</td>
<td>5 months</td>
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<tr>
<td>Reaches</td>
<td>6 months</td>
</tr>
<tr>
<td>Pincer</td>
<td>11 months</td>
</tr>
<tr>
<td>Marks on paper with crayon</td>
<td>12 months</td>
</tr>
<tr>
<td>Stacking two blocks</td>
<td>15 months</td>
</tr>
<tr>
<td>Scribbles spontaneously</td>
<td>18 months</td>
</tr>
<tr>
<td>Self-help</td>
<td></td>
</tr>
<tr>
<td>Cooperates in dressing</td>
<td>12 months</td>
</tr>
<tr>
<td>Doffs hat or socks</td>
<td>15 months</td>
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<tr>
<td>Scoops with a spoon</td>
<td>15 months</td>
</tr>
<tr>
<td>Drinks from a cup with little spillage</td>
<td>18 months</td>
</tr>
<tr>
<td>Spears with a fork</td>
<td>36 months</td>
</tr>
<tr>
<td>Goes to toilet independently</td>
<td>36 months</td>
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<tr>
<td>Dresses independently</td>
<td>48 months</td>
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<tr>
<td>Spreads with a knife</td>
<td>48 months</td>
</tr>
<tr>
<td>Ties shoes</td>
<td>60 months</td>
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<tr>
<td><strong>Social–emotional</strong></td>
<td></td>
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<tr>
<td>Stranger anxiety established</td>
<td>9 months</td>
</tr>
<tr>
<td>Looks when name is called</td>
<td>10 months</td>
</tr>
<tr>
<td>Points to indicate wants</td>
<td>12 months</td>
</tr>
<tr>
<td>Points to declare interest</td>
<td>15 months</td>
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<tr>
<td>Imitates housework</td>
<td>18 months</td>
</tr>
<tr>
<td>Parallel play</td>
<td>24 months</td>
</tr>
<tr>
<td>Interactive play/takes turns</td>
<td>36 months</td>
</tr>
<tr>
<td>Imaginary play</td>
<td>36 months</td>
</tr>
<tr>
<td>Takes turns and shares</td>
<td>48 months</td>
</tr>
<tr>
<td>Group play</td>
<td>48 months</td>
</tr>
<tr>
<td>Board games</td>
<td>72 months</td>
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Neurodevelopmental Disabilities and their Management

Chapter 28

receptive–expressive language disorder, hearing loss, movement disorders, ADHD and consanguinity should be recorded. Non-diagnosed delays in motor, language and academic domains should be noted. Adult-onset psychiatric and neurological disorders should be queried.

The physical examination should be comprehensive. Often it is limited by the child’s age, level of cooperation or ability to comply with tasks. Special attention should be focused on current growth parameters, and somatic and head growth trajectories, head shape and status of fontanelles, facial and other dysmorphisms, congenital anomalies, visceromegaly and neurocutaneous stigmata. The neurological examination should focus on the motor examination. Evaluation of axial and appendicular tone and strength, observation of abnormal postures or movements, focal motor findings and abnormalities of cranial nerve function should be noted. Completion of peg boards, stacking blocks or timed writing tasks is a sensitive measure of fine motor abilities. Reliable examination of cortical sensory functions may not be possible until the child is school age, but coarse estimates are possible. All children who evidence developmental dysfunction should have a formal audiological evaluation and thorough ophthalmological assessment as part of the aetiological evaluation.

The clinical practice guidelines recommend neuroimaging studies, with MRI as the preferred modality. The staging of the imaging may differ, however. In the case of CP or motor delay, MRI should be the first investigation but, in children with global developmental delay or autism, it may be prudent to perform genetic testing first. Routine neuroimaging is not recommended for the evaluation of children with autism unless there is concern about underlying structural malformations, or for children with motor delays unless there are concerns about CP.

MRI of children with CP may show periventricular leukomalacia, hydrocephalus, migrational defects, leukodystrophy, neurodegenerative disorders, or evidence of basal ganglia injury that may be associated with keratitis or metabolic disorders (Accardo et al. 2004). Neuroimaging of children with global developmental delay may show malformations, delayed myelination, or white matter disease, atrophy or heterotopias. Despite the high yields, approximately 15% of children with CP will have unrevealing MR images (Reid et al. 2013). MRI is also recommended for children with global developmental delay. The yield is increased in children who show abnormalities of head size, focal examination or seizures.

Array comparative genetic analysis has replaced high-resolution karyotype and subtelomeric fluorescence in situ hybridisation as the first-line evaluation for children with global developmental delay, children with autism who manifest intellectual disability and children with motor delay who show evidence of other clinical indicators. Array comparative genomic hybridisation (aCGH) allows for the provision of prognosis and recurrence risks, improves access to resources, helps limit further investigations and may alter medical management in many cases (Cameron et al. 2012). It has led to the delineation of novel genetic syndromes associated with developmental delay. The application of microarray analysis to children with CP is just starting to be appreciated (McMichael et al. 2014). Although evaluation of populations of children with CP has not been revealing, individual children with severe CP and intellectual disability have been shown to have abnormal arrays (O’Callaghan et al. 2012).

Chromosomal microarray analysis detects aneuploidies, well-characterised microdeletion/microduplication syndromes, and subtelomeric or other unbalanced chromosomal rearrangements. In addition, aCGH can uncover numerous copy number variants (CNVs) of unclear significance. This method is the most sensitive method for providing an aetiological diagnosis in global developmental delay. It is abnormal in approximately 8% of those with global developmental delay/intellectual disability and about 11% of those with syndromic features (Kang and Koo 2012). Microarray testing has delineated novel genetic syndromes. As experience increases, the CNVs of unclear significance will be further characterised.

Recently, whole-exome sequencing has become clinically available and holds promise for identifying the genetic cause of an increasing number of rare mendelian disorders or highly penetrant new point mutations (Sherr et al. 2013). It has greater resolution than microarray analysis and has yields in 25–30% of patients (Yang et al. 2013). At present its use should be restricted to families who are desirous of additional testing after microarray analysis has been unrevealing, and performed by centres that are able to interpret the findings.

X-linked intellectual disability is estimated to account for 10% of intellectual disability in all patients. Panels that test for genes associated with linked intellectual disability are available and should be obtained in boys who have a strong family history suggestive of X-linked inheritance. DNA testing for Fragile X should be included in the evaluation of children with global developmental delay (Kraan et al. 2013; Monaghan et al. 2013). Finally, mutations in MECP2 are found in 1.5% of girls with moderate/severe global developmental delay/intellectual disability, but the yield in boys is <0.5%.

Sex chromosome aneuploidies (XXX, XXY, XYY) have been associated with language impairment and social difficulties (Bishop et al. 2011; Lee et al. 2012). The prevalence of these disorders in the general population (approximately three in 1000) compared with the prevalence of preschool language disorders (6%) makes the likelihood of a positive result approximately one in 20. If associated with abnormal growth, the likelihood is increased.

Evaluation for inborn errors of metabolism has a low yield without clinical indicators. Non-specific investigation has not been recommended for children with autism, global developmental delay (provided that screening results for newborn infants are normal) or CP. Most of the common metabolic disorders can be detected on a screen of newborn infants, and the neurologist should be familiar with the local screening practice. Congenital disorders of glycosylation, cholesterol metabolism (e.g. Smith–Lemli–Opitz syndrome), mitochondrial disorders and the creatine transporter defect
are not part of the screening. Screening of newborn infants for peroxisomal disorders is possible but not widely applied as yet.

EEG is recommended only if there are clinical findings to suggest epilepsy or a specific epilepsy syndrome (see Chapter 16).

Each of the parameters has some additional recommendations. Testing for lead has been recommended for children with autism or those with global delay who have pica. Creatine phosphokinase testing and thyroid function tests have been endorsed for children with motor delays — the latter because of the possibility of delayed onset or acquired thyroid dysfunction. Evaluation for coagulation disorders should be undertaken in children with hemiplegia.

**MANAGEMENT OF DEVELOPMENTAL DELAY/NEURODEVELOPMENTAL DISABILITIES**

Physicians assume several roles in the management of developmental delay. Primary prevention, early diagnosis, confirmation of the diagnosis, aetiological evaluations, delineation of coexisting conditions, interdisciplinary management, treatment, monitoring and advocacy are some of the roles that may be assumed by physicians. Some of these are more typical for primary care providers whereas others are assumed by consultants. However, the choice of which roles to assume is very much an individual decision.

Primary prevention has been effective in decreasing the prevalence of neurodevelopmental disabilities. Preconceptual provision of folate supplements has decreased the prevalence of spina bifida. Congenital rubella and measles encephalitis have become rare disorders because of effective immunization programmes. The incidence of bacterial meningitis has also decreased where there has been effective implementation of immunisation programmes. Physicians have been instrumental in movements to decrease the lead content of gasoline, ensure proper restraint systems for transporting infants and young children, and advocate for safe practices that decrease the chances of significant injury at the playground.

Universal screening of newborn infants, universal hearing assessment of newborn infants and programmes of developmental surveillance and screens, such as that developed by the American Academy of Pediatrics, are examples of secondary prevention. These programmes allow for early identification and early diagnosis, in the hope of providing interventions that ameliorate the adverse effects of the targeted disorders.

The evaluation and diagnosis of the child who presents with developmental delay/dysfunction are a traditional role assumed by healthcare providers. Often a preliminary diagnosis is suggested and the health provider considers alternative diagnoses, then facilitates the acquisition of additional information through which the diagnosis can be confirmed. This process is applied not only to the functional/developmental diagnosis but also to the aetiological diagnosis.

Failure to recognise significant coexisting conditions is a common reason for failed management programmes. As noted above, neurodevelopmental disabilities often occur multiply. To develop a successful, comprehensive management programme, significant coexisting conditions must be identified, diagnosed and incorporated into it, for example, the management of a preschool child with ADHD would change significantly when her underlying dyslexia has been diagnosed (Kube and Shapiro 1996).

Comprehensive management programmes differ from therapy, in that therapy focuses on the disease whereas a comprehensive management programme must not only address the disorder but also take into account the strengths and challenges of the individual, the supports (e.g. financial, cultural, linguistic, mental health) that a family may require to provide the programme, and the capacity of the community to meet the needs of the individual and the family. Comprehensive management programmes are by nature multidisciplinary. Often they have several goals with multiple objectives that have been established by several decision-makers. Programmes may span multiple agencies (e.g. school, church and government) and involve numerous service providers. When done well multidisciplinary management programmes set priorities, coordinate care and are individualised. When done poorly there is confusion, frustration and suboptimal outcomes. Health providers can help the process by guiding the prioritisation of goals, monitoring progress in the programme and supporting the family.

Comprehensive management programmes have the following three goals: to address impairments that are caused by anatomical or physiological derangements, to minimise functional limitations that arise from the impairments and to optimise the individual’s ability to participate in society. A comprehensive multilevel management plan that addresses all the abilities and challenges of a child with a neurodevelopmental disability can be difficult to construct. We have proposed a model that defines a set of domains that ensures that major important elements are not neglected. For each of the domains the practitioners should ask “What is the likely adult outcome in this area?” and “What is needed to optimise function in this domain?” The model consists of the following ten points:

1. Maintenance of physiological stability, e.g. ensuring hydration and necessary calories, control of seizures, recognising and treating sleep apnoea and gastro-oesophageal reflux, and monitoring for medication toxicity.
2. Nursing care: skin, bowel, bladder care; techniques for feeding; positioning, seating and bracing.
3. Activities of daily living: how the individual will feed, dress, bathe and toilet him- or herself.
4. Communication: How will the individual make his or her needs known to others? Will he or she be an oral communicator, use a pictorial system or require technology?
5. Mobility: Will this person walk? What environmental modifications will be required to use a wheelchair at home or in the community? Is power mobility indicated?
6. Transport: What is the method by which this person will be transported? Can this child use standard transport methods safely or will substantial modifications be required?
7. School/work: Will this person be able to function in a general setting with modifications or will a special setting be required? What adaptations will be required to prevent his or her disability from causing secondary difficulties with educational or work achievement?
8. Leisure, play and socialisation: If a child has significant motor or cognitive dysfunction what adaptations will be required to enable social interactions? If a child is not a candidate for team activities, what individual or non-age-segregated activities may be instituted.
9. Behaviour: What are the behaviours that impede the child’s participation and how should they be addressed? What is the likely impact on adult function?
10. Living: Could the complexity of children’s care prevent them from living with their family? What supports are required to keep the child in the home? Where will this person live as an adult? Will the person be independent? What accommodations will need to be planned if the person is not?

This model is most useful for children with complex needs, but for children with mild developmental delays, who are otherwise healthy, the first six domains can be addressed quickly.

Physicians continue to provide medical therapies for people with neurodevelopmental disabilities. The range of pharmacological and surgical treatments for individuals with neurodevelopmental disabilities has increased markedly. The range of approaches for epilepsy has widened to include dietary, surgical and pharmacological agents. Spasticity may be addressed with pharmacological agents administered in a variety of ways, such as nerve blocks, in addition to physical and surgical modalities. There is a continuous stream of new agents to deal with behavioural issues (Handen and Gilchrist 2006; Kaplan and McKracken 2012).

Traditionally, the pharmacological approaches to neurodevelopmental disabilities have been non-specific and have helped by addressing issues that arose from the neurodevelopmental disability. The advances in genetics have led to a new understanding of the biology of neurodevelopmental disabilities, with the potential for targeted pharmacological interventions. Studies of targeted pharmacotherapy are under way to determine whether the course of selected neurodevelopmental disabilities can be altered or cured (Hampson et al. 2012).

Advocacy is a major role assumed by physicians and other health providers, and may occur at multiple levels. At the most basic level, the advocacy may be facilitating the family’s ability to obtain services through referrals, enabling the family to be educated about the child’s disorder through parent groups or websites for their specific disorder/syndrome, writing necessary letters or making phone calls. Becoming involved in the community to develop educational, recreational and leisure programmes for children with disabilities, and educating providers of other disciplines, are additional roles that physicians may assume. Finally, physicians may work with others, either through their professional organizations or together with other disciplines, to effect systemic changes that benefit all people with a developmental disability.

Monitoring is a critical aspect of management. The primary objective of monitoring is to ensure that the prescribed programme is working. Failure of a treatment programme may be due to one of the following: a wrong diagnosis, an incomplete diagnosis, the wrong therapy, (incorrect administration of therapy, insufficient therapy, conflicting therapies, therapist factors, non-compliance, inability to generalise to real-life situations, incomplete/insufficient parent education, competing family factors, changing needs of the patient, age/maturational effects and insufficient resources. The needs of children and their families change over time. As a result, children’s health, learning, and adaptive and behavioural goals must be reassessed and developmentally based. Monitoring visits also afford the health provider an opportunity to answer questions raised by the family, address issues that have arisen as a result of the child ageing (e.g. school demands), prepare caregivers about anticipated future changes that will occur as the child ages (e.g. onset of menses), deal with considerations that need to take place as parents age (e.g. estate planning or guardianship) or deliver new information about the child’s condition. A periodic review should include information about the child’s health status, as well as his or her functioning at home, at school and in other social contexts. Other information, such as formal psychoeducational testing, may be needed. Monitoring visits should take place at times when rapid change is expected, when there are transitions, if there are new symptoms or if there is insufficient progress.

CONCLUSION

Development is the functional expression of brain maturation. It is ordered, predictable and predictive. ‘Neurodevelopmental disabilities’ is a term used to describe syndromes of aberrant development, and may result from a wide range of aetiologies that cause diffuse brain dysfunction. Often, neurodevelopmental disabilities occur multiply. The dysfunction may be appreciated immediately or may not be appreciated until the demands of the situation exceed the individual’s abilities. Comprehensive management programmes for children with neurodevelopmental disabilities must be comprehensive, prioritised and coordinated to be successful.

REFERENCES


# Autism Spectrum Disorder and Autistic-Like Conditions

*Anne O’Hare and Roberto Tuchman*

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Autism Spectrum Disorder and Autistic-Like Conditions

Anne O’Hare and Roberto Tuchman

DEFINITION

When autism was first described in 1943 by Kanner, he described 11 children with an inability to relate to other people, but a heightened ability to attend to change in the non-social environment (Kanner 1943). Autism spectrum disorders (ASDs) now refer to a behaviourally defined group of neurodevelopmental disorders that are characterised by these social–communicative deficits combined with restricted and repetitive behaviours and interests. Autism was incorporated into The Diagnostic and Statistical Manual of Mental Disorders (DSM) only by 1980. Now, the recently published DSM-5 (American Psychiatric Association 2013) has moved away from this categorical description to a developmentally based, dimensional conceptualisation of ASD (Lord and Jones 2012). In both the DSM-5 and the upcoming International Classification of Diseases, 10th (ICD 10) (WHO 2015), all children meeting diagnostic criteria are regarded as having an ASD. The earlier subtypes of autism have been replaced by these recent classifications which place language function as both part of the social–communicative domain and a modifier of autism symptomatology.

There are several important points to consider in the diagnosis of an individual with ASD. First, the diagnosis of an ASD remains behaviourally based, and there are no current neurobiological markers or specific neurological tests used to make the diagnosis. Second, ASD as a spectrum disorder includes differences in the severity and presentation of the symptoms that define it, which can range from severe disabling symptoms, such as lack of any verbal or non-verbal communication or severe repetitive self-injurious behaviours, to individuals who speak fluently but whose conversational skills are restricted to specific subjects or who are obsessive about particular subjects such as the weather or maps. Third, the concept of ‘the autisms’ has been proposed to conceptualise the diverse aetiologies that are associated with and may lead to an ASD (Geschwind and Levitt 2007). It is important to appreciate that aetiology does not define whether an individual does or does not have an ASD, so, for example, an individual may have fragile X syndrome (FXS) as an aetiology for an ASD, but many individuals with FXS do not meet all the criteria for an ASD despite their social interactional difficulties. Last, and as is discussed further below, there are multiple modifiers, of which level of intelligence is a major one, which differentiate the clinical presentation, developmental trajectory and outcome of ASDs (Lai et al. 2013; Anderson et al. 2014).

In the DSM-5 the two core domains used to diagnose ASDs are the following: (1) persistent deficits in social communication and interaction across multiple domains and (2) restricted, repetitive patterns of behaviour, interest or activities. A major change in the present DSM criteria has been to include language deficits within the broader social communication domain, as well as using level of language function as a modifier to describe level of function in ASDs. The overlap of ASDs with developmental disorders of language has historically been an important subject of interest and research (Savage 1968; DeMyer et al. 1981; Rapin 1998; Dominick et al. 2007). In the younger child first presenting with a language disorder severely affecting receptive language, who has no expressive language, the differentiation at a clinical level of a diagnosis of severe expressive–receptive language disorder versus ASD can be extremely difficult, especially in light of the fact that the child might have both diagnoses. It is now recognised that there are different types of language disorders in ASDs (Rapin et al. 2009) and that there are significant genetic overlaps between ASDs and disorders of language (Muhle et al. 2004; Abrahams and Geschwind 2008). The importance of recognising and describing speech and language subtypes in children with ASDs has previously been underappreciated (McCann et al. 2007).

A specific group of children who fall under the social communication spectrum are those with semantic–pragmatic language deficit disorders. This group of children, if they do not have repetitive and restricted patterns of behaviours, interests or activities, are referred to as having a social communication disorder, under language disorders, in the new DSM classification system. They were initially described in the 1980s as having difficulties with the semantic and pragmatic use of language without meeting the full criteria for ASDs, but having social–communicative deficits that overlap with those of ASDs (Bishop 1989). Deficient pragmatics, meaning the communicative use of language, especially non-verbal
with pragmatics or receptive language impairment, would as having developmental language disorders, especially those that some children who in the past might have been classified as having Asperger syndrome, another group currently be classified with ASDs (Rapin and Dunn 2003). There can be substantial diagnostic challenges in differentiating these two conditions, particularly as the restricted repetitive behaviours may manifest in the idiosyncratic and repetitive language used. In addition, semantic–pragmatic issues are common in high functioning individuals with ASDs, including those with Asperger syndrome, another group under the larger category of ASDs (Dennis et al. 2001; Losh and Capps 2003; Loukusa et al. 2007), and pragmatic difficulties are universal in ASDs (Rapin 1998). It has been suggested that some children who in the past might have been classified as having developmental language disorders, especially those with pragmatics or receptive language impairment, would currently be classified with ASDs (Bishop et al. 2008).

Social communication deficits in ASDs must include deficits in social–emotional reciprocity, non-verbal communication, and developing, maintaining and understanding relationships. The range of behaviours that define the domains of social emotional reciprocity includes lack of social initiation and response to social interactions, reduced sharing of interests with others, reduced emotional reciprocity, awkward or abnormal social interactions and reduced or lack of conversational skills for developmental age. Deficits in non-verbal communication range from poor use of eye gaze and body language, to lack of gestures, facial expressions and other non-verbal communication skills. Deficits in developing and maintaining relationships include a wide range of behaviours such as an inability to make friends, despite wanting to, an absence of interest in peers and adapting poorly to new social situations.

Pragmatics, characterises children with ASDs (Rapin and Dunn 2003). There can be substantial diagnostic challenges in differentiating these two conditions, particularly as the restricted repetitive behaviours may manifest in the idiosyncratic and repetitive language used. In addition, semantic–pragmatic issues are common in high functioning individuals with ASDs, including those with Asperger syndrome, another group under the larger category of ASDs (Dennis et al. 2001; Losh and Capps 2003; Loukusa et al. 2007), and pragmatic difficulties are universal in ASDs (Rapin 1998). It has been suggested that some children who in the past might have been classified as having developmental language disorders, especially those with pragmatics or receptive language impairment, would currently be classified with ASDs (Bishop et al. 2008). Social communication deficits in ASDs must include deficits in social–emotional reciprocity, non-verbal communication, and developing, maintaining and understanding relationships. The range of behaviours that define the domains of social emotional reciprocity includes lack of social initiation and response to social interactions, reduced sharing of interests with others, reduced emotional reciprocity, awkward or abnormal social interactions and reduced or lack of conversational skills for developmental age. Deficits in non-verbal communication range from poor use of eye gaze and body language, to lack of gestures, facial expressions and other non-verbal communication skills. Deficits in developing and maintaining relationships include a wide range of behaviours such as an inability to make friends, despite wanting to, an absence of interest in peers and adapting poorly to new social situations.

The domain of a restricted, repetitive pattern of behaviours, interests or activities needs to be manifested by at least two of the components of criteria B (Table 29.1). Criteria C and D define symptoms from early childhood and functional impact.

The domains that define ASDs are therefore dimensional and the degree of severity is an important part of the characterisation. It may range from requiring minimal support, through requiring substantial support to requiring very substantial support. In addition, symptoms of ASDs must be present in the early developmental period, although they may not become fully apparent or manifest until social demands exceed that individual’s capacities. This latter point is especially relevant in those with ASDs and good intellectual skills, in whom the intellectual skills allow them to learn strategies that mask their social skills deficits. In some highly intelligent individuals with ASDs there is controversy as to whether ‘autistic spectrum condition’ may be a more appropriate term because the social skills deficits in these individuals may not cause significant clinical impairment in current functioning, which is a requirement in making the diagnosis of ASD. Intellectual disability or, in those aged <5 years, global developmental delay (GDD) commonly overlap and coexist with ASDs; to make the diagnosis of both disorders the behavioural symptoms of ASDs cannot be better explained by intellectual disability or GDD and the social communication skills should be below those expected for the general developmental level (Riou et al. 2009).

In summary, the conceptualisation of ASDs in the new DSM and the forthcoming ICD-11 classification systems addresses the heterogeneity and dimensional nature of this
group of disorders through the use of specifiers or modifiers. The move away from subgroups, which had appeared in previous iterations of DSM/ICD, is now replaced by specific descriptions of cognitive level, degree of language impairment, or other neurodevelopmental or behavioural disorder such as ASD with attention-deficit-hyperactivity disorder (ADHD), association with known medical conditions, e.g. epilepsy, genetic such as Rett or FXS or environmental contributors such as social deprivation, perinatal factors or exposure to teratogens (Lai et al. 2013) (Table 29.2).

<table>
<thead>
<tr>
<th>Category</th>
<th>Specifier</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental pattern</td>
<td>Pattern of atypical development</td>
<td>1. Age and pattern of onset/regression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Trajectory of development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Language onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Hyperlexia</td>
</tr>
<tr>
<td>Gender</td>
<td>Biological gender</td>
<td>Male/female</td>
</tr>
<tr>
<td></td>
<td>Gender-adjusted autistic features</td>
<td>Statistical characterisation of autistic trait (e.g. percentile) relative to gender-specific norms</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>Co-occurring condition</td>
<td>1. Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Macrocephaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Gastrointestinal disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Immune disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Hyperserotoninaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Attention-deficit–hyperactivity disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Anxiety disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Depressive disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Tics/Gilles de la Tourette syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Obsessive–compulsive disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. Schizophrenia spectrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Dyslexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13. Personality disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14. Self-injurious behaviours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Sleep disruption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16. Eating disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17. Gender dysphoria</td>
</tr>
<tr>
<td>Taxonomic formulation</td>
<td></td>
<td>1. Asperger syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. ‘Aloof’/‘passive’/‘active but odd’/‘loners’ groups</td>
</tr>
<tr>
<td>Motor abnormality</td>
<td></td>
<td>1. Types of motor stereotypy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Coordination disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Dyspraxia</td>
</tr>
<tr>
<td>Cognitive profile</td>
<td>Intelligence</td>
<td>1. IQ profile (including discrepancy among subtests)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Savant memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Savant spatial skills</td>
</tr>
<tr>
<td>Current language (structural properties)</td>
<td></td>
<td>1. Phonological/phonetic processing (including articulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Prosodic processing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Morphological processing</td>
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<tr>
<td></td>
<td></td>
<td>4. Syntactic processing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Semantic processing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Receptive versus expressive abilities</td>
</tr>
<tr>
<td>Social cognition</td>
<td></td>
<td>1. Emotion perception and understanding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Face recognition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Emotional contagion</td>
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<tr>
<td></td>
<td></td>
<td>4. Social orienting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Social and non-social reward processing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Affective empathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Sympathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Joint attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Pretend play</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Theory of mind/mental perspective taking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. Self-referential cognition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Alexithymia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13. Metacognitive awareness</td>
</tr>
</tbody>
</table>

Continued
Last, the DSM now includes catatonia as one of the specific conditions associated with ASDs.

Conceptualisation of ASDs, as a consequence of variation in levels of dysfunction in social communication and restricted repetitive behaviours and interests, impacted by environmental, medical, genetic and other behavioural disorders, and often without a singular genetic, neural or cognitive explanation (Happe and Ronald 2008), goes a long way towards clarifying and defining the ill-defined boundaries and limitations of previous classification systems for ASDs.

### Table 29.2 A preliminary expanded (but not exhaustive) list of specifiers, towards the identification of subgroups (continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Specifier</th>
<th>Example</th>
</tr>
</thead>
</table>
| Cognitive profile          | Executive function                 | 1. Cognitive flexibility  
2. Planning  
3. Inhibitory control  
4. Attention shifting  
5. Working memory  
6. Time perception  |
| Bottom-up perceptual       | processing                         | 1. Global–local perceptual processing  
2. Low-level perceptual function and discrimination  
3. Synaesthesia  |
| Top-down information       | processing                         | 1. ‘Central coherence’ (global–local contextual processing)  
2. ‘Systemising’ (drive to construct rule-based systems, ability to understand rule-based systems, knowledge of factual systems) |
| Genetics                   | Syndromic autism                   | 1. Fragile X syndrome  
2. Rett syndrome  
3. Tuberculosis complex  
4. Timothy syndrome  
5. Down syndrome  
6. Phenylketonuria  
7. CHARGE syndrome  
8. Angelman syndrome  
9. PTEN macrocephaly syndrome  
10. Joubert syndrome  
11. Landau–Kleffner syndrome  
12. Prader–Willi syndrome  
13. Smith–Lemli–Opitz syndrome  
14. Neurofibromatosis |
| Familial aggregation       |                                    | Simplex vs multiplex |
| Gene-level variations      |                                    | For example, ASTN2, AVPR1A, CACNA1C, CACNA1G, CDH8, CDH9, CDH18, CNTN4, CNTNAP2, DISC1, DPP6, DPYD, EN2 (Engrailed 2), FMR1, FOXP2, GABRA4, GABRB3, GluR6, GRIK2, GSTD1, HOX1, HOXB1, ITGB3, MACROD2, MADCAM1, MAPK3, MBDS, MECP2, MET, NLGN3, NLGN4X, NRXN1, NRXN3, OXTR, PRKCB1, PRL, PRLR, PTCHD1/PTCHD1AS, PTEN, RELN (Reelin), SEMAS5A, SERT (SLC6A4), SHANK1, SHANK2, SHANK3 (ProSAP2), SLC25A12, TSC1, TSC2, UBE3A |
| Copy number variations     |                                    | (Specify known ASD-association status, genetic loci and deletion/duplication) |
| Environmental risks        | Social deprivation                 | Early social isolation or neglecta |
| Environmental risk factor  | exposure                           | 1. Rubella virus infection during gestationa  
2. Valproic acid exposure during gestationa  
3. Antidepressant exposure during gestationa |

aFrom Lai et al. (2013).
Specify timing: gestational weeks X to Y.
CHARGE, coloboma, heart defect, atresia choanae (also known as choanal atresia), retarded growth and development, genital abnormality and ear abnormality; PTEN, phosphatase and tensin homologue.

### PREVALENCE

ASDs are common (Elsabbagh et al. 2012) and affect just over 1% of the UK population, established by active ascertainment studies of 9-year-old children (Baird et al. 2006) and adults (Brugha et al. 2011). Estimates of prevalence in the United States (Bertrand et al. 2001; Centers for Disease Control and Prevention, Autism and Developmental Disabilities Monitoring Network 2014) have recently been reported as high as one in 68. However, it has been argued that this may be an over-estimate.
based on clinical and educational records (Mandell and Lecavalier 2014). Cross-sectional, active ascertainment studies identify many children and adults who were previously unrecognised as having ASDs. This similarity in prevalence between children and adults is in keeping with the hypothesis that increases in prevalence rates observed follow changes in diagnostic practice. In the general population, social skills plot out as a continuous distribution of abilities and deficits (Constantino and Todd 2000; Constantino et al. 2000, 2003a, b) and there is a continuum of the genetics of reciprocal social interaction, which is the core and distinguishing feature of ASDs (Walters et al. 1990). The continuum of social skills in the general population is consistent with what has been termed the ‘broader autism phenotype’ (BAP) (Bolton et al. 1994). Studies suggest that there are ‘autistic traits’ in families of individuals with ASDs that are subclinical, and index the BAP (Piven et al. 1997; Bailey et al. 1998; Constantino et al. 2000; Scheeren and Stauder 2008). The prevalence of this extended phenotype is four to five times greater than ASDs.

**SEX**

There is a strong male preponderance in ASDs and it is unclear whether this arises secondary to a true biological vulnerability for males, or is a referral or diagnostic artefact (Jeste and Geschwinda 2014; Ribet and Matson 2011; Rutherford et al. 2016). Historically, the male:female ratio was reported as 3:4:1 (Fombonne 2005a), but more recent population studies have reported a smaller ratio of 2.6:1 (Idring et al. 2012; Centers for Disease Control and Prevention, Autism and Developmental Disabilities Monitoring Network 2012). The large sample from the Autism and Developmental Disabilities Monitoring (ADDM) network for ASD surveillance, conducted in 13 different sites across the United States, has been particularly informative in the debate over sex balance in diagnosis. Giarelli et al. (2010) showed, in their population, that there was no difference by sex in the average age of the first evaluation or time of diagnosis, but that girls were less likely than boys to receive a documented diagnosis of ASD. However, the study identified that these girls had features in keeping with ASDs but they had been assigned diagnoses such as intellectual disability instead.

**ASD**s** AND INTELLECTUAL DISABILITY**

Intellectual disability accounts for the most salient group differences in individuals with ASDs which are noted when the groups are categorised on IQ (Witwer and Lecavalier 2008). The initial descriptions of ASDs found a high correlation of prevalence with the severity of intellectual disability, with the vast majority of children with severe intellectual disability manifesting the ‘autistic triad’ (Wing and Gould 1979; Wing 1981). Recent epidemiological studies suggest that approximately 40–60% of children with ASDs have some degree of intellectual disability (Chakrabarti and Fombonne 2005b; Charman et al. 2011). In addition, the more you look for autistic traits among populations of children with low IQ, the more likely you are to recognise them. Children with chromosomal and single-gene disorders with low IQ will show approximately a third affected by an ASD (Skuse 2007; Moss et al. 2013).

Intellectual ability not only accounts for the differences among individuals and groups of children within the autism spectrum, but is also an important factor in moderating the expression of ASDs (Matson et al. 2008a, b; Wilkins and Matson 2009), conferring risk for their coexistence with other neurological disorders such as epilepsy (Tuchman et al. 2009), as well as predicting outcome (Billstedt et al. 2007; Eaves and Ho 2008; Helt et al. 2008; Woolfenden et al. 2012a; Anderson et al. 2014). An ASD with associated intellectual disability is more likely to be associated with a specific genetic disorder and many have termed this ‘syndromic’ ASD, but it is best to define ASD if the behavioural criteria are met, and then specify the genetic or medical condition associated with it. This approach is consistent with the notion that ASD is a behavioural clinical construct and, for some children, an underlying aetiology can be increasingly identified. There are at least over 100 underlying genetic aetiologies of ASDs presently recognised and this is rapidly expanding [National Institute for Health and Care Excellence (NICE) 2011; Dawson 2010]. This avoids the misconception for families that, if no underlying cause is established, then the diagnosis of ASD itself may be called into question.

**CLINICAL FEATURES OF ASD**s**

**ASD**s** in the Early Years**

General developmental warnings of possible ASDs in preschool children (Landa 2008) have been summarised in best practice protocols. Warreyn et al. (2014) stresses the importance of social–communicative abilities, both as early and important features seen in preschool children with ASDs and as areas for intervention because of their importance as treatment goals. She emphasises that there are three critical abilities for infants, toddlers and preschool children, as follows: imitation, joint attention and play. Problems with imitation deviate from the typical picture at 18 months in children who go on later to have an ASD diagnosis. Joint attention is a very important early deficit for children with ASDs. They may be able to show passive joint attention, whereby they follow gaze or even imperative joint attention, which is when the child is making a request, but it is the declarative joint attention, that is, the social function of sharing an interest in something with someone else, that is particularly disrupted. This is related in longitudinal studies to reduced development of later language and ‘theory of mind’, that is, the ability to impute the thoughts of others.

Play is also impoverished in infants and preschoolers with ASDs. Relational and combinational play, that is, placing one object with another, emerges in typical development when a
child is aged around 14 months. This is followed 3–6 months later by symbolic play, which is the ability to create imaginary events. Symbolic play takes a number of different forms, so the child may substitute one object for another imagined object or person, or attribute a property to an object or person, such as animating miniatures, or make reference to an object person or substance that is not actually present at the time. By the age of 20 months, the child can put this symbolic play into a meaningful sequence. Children with ASDs have deficits in basic forms of play. An early lack of symbolic play, when combined with a deficit in joint attention, is highly predictive for a later diagnosis of an ASD.

A number of interventions target imitation, joint attention and play, such as the Early Start Denver model (Dawson et al. 2010). Multicentre international studies of infants at high risk of ASDs, because of an affected sibling, have identified that the trajectory of development towards the symptomatology of ASDs is after age 1 year. Early features include reduced babbling and subtle anomalies of social responsiveness, such as difficulty in emerging gesture, joint attention, imitation and response to name. This area remains a very active research endeavour and some of the subtle infant features that will be predictive of later ASD remain to be fully delineated (Jones et al. 2014).

Infants who are later diagnosed with ASDs may still have symptoms when aged <1 year that are due to their accompanying GDD. The most common presentation of lack of speech development and absence of developmental milestones is as important as positive symptomatology, especially in younger children. Significant restricted repetitive behaviours may be difficult to distinguish in the toddler years from those that are developmentally appropriate, or they may be less salient. Recent evidence-based guidelines examined the accuracy of signs and symptoms to predict ASD and reported that, across all children’s age groups, insistence on certain routines and rituals is only 50% [95% confidence interval (CI) 35, 56] sensitive. In contrast, failure in preschool children to perform ‘protodeclarative’ pointing, that is, the child trying to share interest, along with reduced gaze monitoring and pretend play, was 100% sensitive and specific (NICE 2011).

A number of recent evidence-based guidelines have also delineated screening instruments for ASDs [New York State Department of Health, Bureau of Early Intervention 1999; Le Couteur 2003; Scottish Intercollegiate Guidelines Network (SIGN) 2007; Ministries of Health and Education 2008; Academy of Medicine Singapore 2010; NICE 2011, 2012; Hathorn et al. 2014] (Tables 29.3 and 29.4). In general, even with high-risk populations of children, these instruments are primarily useful as surveillance instruments because their properties of sensitivity and specificity are not sufficient for them to be used to rule an ASD in or out. They can be useful to structure the concerns, symptoms and signs and the Modified Checklist for Autism in Toddlers (M-CHAT; Robins et al. 2009) shown in Table 29.5 is freely available in the public domain and does not require specialist ASD expertise.

### Table 29.3  Best practice protocol for early screening of young children for autism spectrum disorders (ASDs) by pediatric primary care providers

<table>
<thead>
<tr>
<th>Clinical clues for possible ASD in pre-school children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay or absence of spoken language</td>
</tr>
<tr>
<td>Looks through people; not aware of others</td>
</tr>
<tr>
<td>Not responsive to other people’s facial expression/feelings</td>
</tr>
<tr>
<td>Lack of pretend play; little or no imagination</td>
</tr>
<tr>
<td>Does not show typical interest in or play near peers purposefully</td>
</tr>
<tr>
<td>Lack of turn-taking</td>
</tr>
<tr>
<td>Unable to share pleasure</td>
</tr>
<tr>
<td>Qualitative impairment in non-verbal communication</td>
</tr>
<tr>
<td>Does not point at an object to direct another person to look at it</td>
</tr>
<tr>
<td>Lack of gaze monitoring</td>
</tr>
<tr>
<td>Lack of initiation of activity or social play</td>
</tr>
<tr>
<td>Unusual or repetitive hand and finger mannerisms</td>
</tr>
<tr>
<td>Unusual reactions, or lack of reaction, to sensory stimuli</td>
</tr>
</tbody>
</table>

Reproduced with permission from New York State Department of Health, Bureau of Early Intervention (2013).

### Autistic Regression

The clinical feature of regression of skills in paediatric neurology is usually an indication for investigation of an acquired disease such as a neurometabolic disorder or paroxysmal condition such as Landau–Kleffner syndrome dysphasia. However, regression in ASDs is usually an exception. In autistic regression, there is no confirmed aetiology, no increased incidence of epileptic seizures and no indications to investigate with EEG imaging or neurometabolic screening. Therefore, it is very important to recognise this dramatic symptom of ASDs, which has been termed a ‘red flag’ for these disorders (Filipek et al. 2000; Goldberg et al. 2003; Lord et al. 2004; Luyster et al. 2005; Walters et al. 2005; Werner et al. 2005; Baird et al. 2008; Meilleur and Fombonne 2009).

Regression in ASDs usually involves loss of social communicative behaviours and, if other aspects are lost, such as motor skills, further neurological investigation should be considered. The regression can take the form of a very abrupt change in a child’s development and behaviour; in other cases it is a more gradual change, more in the nature of a stasis (Fountain et al. 2012). It is generally described as happening before age 2 years (Barger et al. 2013), although the mean age for retrospective capture of the regression in a large cross-sectional study was 25 months (Baird et al. 2008). It is often defined as the loss of language after the first three to five-word stage of acquisition, and there is also usually a loss of non-verbal communication such as gestures, along with decreased use of eye contact to regulate social interaction; there is also some social withdrawal and lack of social interest, and sometimes a loss of play skills. If the child has not reached the three- to five-word stage of language development, there may also be regression of babble and protowords, along with regression in...
## Table 29.4  Accuracy of signs and symptoms to predict autistic spectrum disorders (ASDs)

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>Quality assessment</th>
<th>Number</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies</td>
<td>Design</td>
<td>Limitations</td>
</tr>
<tr>
<td>Preschool children (0–5 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to perform protodeclarative pointing, gaze monitoring and pretend play</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>Failure to perform protodeclarative pointing or protodeclarative pointing and pretend play</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>No pretend play</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>No functional play</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>No facial concern in response to others distress</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>No attention to distress</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>Atypical use of object</td>
<td>1</td>
<td>Con obs</td>
<td>Some</td>
</tr>
<tr>
<td>Lack of orienting to name</td>
<td>2</td>
<td>Con obs</td>
<td>Some</td>
</tr>
</tbody>
</table>

Reproduced with permission from National Institute for Health and Care Excellence (2011).

CI, confidence interval; Con obs, contemporary observations; NA, not applicable.
social interest and variable rates of regaining of skills. There should be very careful clinical evaluation to consider whether this could be a presentation of Rett syndrome in girls (Baird et al. 2008). Therefore, in the absence of an acute neurological event, regression in a child aged 1–3 years should be a ‘red alert’ for assessment of ASDs and signals an altered trajectory of development (Filipek et al. 2000).

Regression is not associated with epileptic seizures or gastrointestinal problems, but is associated with higher rates of autistic symptoms and a deviation in developmental trajectory. In the South Thames study in the United Kingdom, it affected 30% of children with what was described as core autism and 8% with a broader ASD; it was seen only in the 3% of children who had developmental problems without an ASD, and these two children both had various neurological precedents (Pickles et al. 2009).

Autistic regression is very rare before the age of 1 year and so, if clinicians are faced with this timing, they need to think of other precipitants such as the autism-like regression, which can accompany infantile spasms with tuberous sclerosis and usually come on between age 4 and 10 months (Desguerre et al. 2008). Also treatable conditions such as biotinidase deficiency (Weber et al. 2004) should be considered, as well as noting important features in the clinical examination, such as the trajectory of reducing occipital frontal diameter and

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### Table 29.5 Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R)

Please answer these questions about your child. Keep in mind how your child usually behaves. If you have seen your child do the behaviour a few times, but he or she does not usually do it, then please answer no. Please circle yes or no for every question. Thank you very much.

1. If you point at something across the room, does your child look at it? (For example, if you point at a toy or an animal, does your child look at the toy or animal?) Yes No
2. Have you ever wondered if your child might be deaf? Yes No
3. Does your child play pretend or make-believe? (For example, pretend to drink from an empty cup, pretend to talk on a phone, or pretend to feed a doll or stuffed animal?) Yes No
4. Does your child like climbing on things? (For example, furniture, playground equipment or stairs) Yes No
5. Does your child make unusual finger movements near his or her eyes? (For example, does your child wiggle his or her fingers close to his or her eyes?) Yes No
6. Does your child point with one finger to ask for something or to get help? (For example, pointing to a snack or toy that is out of reach) Yes No
7. Does your child point with one finger to show you something interesting? (For example, pointing to an airplane in the sky or a big truck in the road) Yes No
8. Is your child interested in other children? (For example, does your child watch other children, smile at them or go to them?) Yes No
9. Does your child show you things by bringing them to you or holding them up for you to see – not to get help, but just to share? (For example, showing you a flower, a stuffed animal or a toy truck) Yes No
10. Does your child respond when you call his or her name? (For example, does he or she look up, talk or babble, or stop what he or she is doing when you call his or her name?) Yes No
11. When you smile at your child, does he or she smile back at you? Yes No
12. Does your child get upset by everyday noises? (For example, does your child scream or cry to noise such as a vacuum cleaner or loud music?) Yes No
13. Does your child walk? Yes No
14. Does your child look you in the eye when you are talking to him or her, playing with him or her or dressing him or her? Yes No
15. Does your child try to copy what you do? (For example, wave bye-bye, clap or make a funny noise when you do) Yes No
16. If you turn your head to look at something, does your child look around to see what you are looking at? Yes No
17. Does your child try to get you to watch him or her? (For example, does your child look at you for praise, or say 'look' or 'watch me'?) Yes No
18. Does your child understand when you tell him or her to do something? (For example, if you don’t point, can your child understand ‘put the book on the chair’ or ‘bring me the blanket’?) Yes No
19. If something new happens, does your child look at your face to see how you feel about it? (For example, if he or she hears a strange or funny noise, or sees a new toy, will he or she look at your face?) Yes No
20. Does your child like movement activities? (For example, being swung or bounced on your knee) Yes No

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onset of the midline hand stereotypies that can characterize Rett syndrome (Lam et al. 2000). In addition, there can be developmental ‘setbacks’ emerging as early as age 16 months for children dealing with a profound visual impairment (Dale and Salt 2008).

If there is loss of well-established verbal language skills after age 30–36 months, an epileptic encephalopathy, such as continuous spike waves during slow-wave sleep epileptic aphasia or Landau–Kleffner syndrome should be considered (Tuchman 2009; Deonna and Roulet-Perez 2016). These conditions may have very subtle outward signs of seizures, so the possibility that this is a paroxysmal disorder may be overlooked; in the case of Landau–Kleffner syndrome dysphasia, no seizures may be evident at all. Some of the features of Landau–Kleffner syndrome dysphasia in the expressive language, such as naming difficulties, verbal paraphrasias, telegraphic speech and neologisms, have a different quality to the stereotyped echolalic speech of children with ASDs, but there is some degree of overlap and mutism can occur in both regressions.

**ASDs in School-Aged Children and Young People**

Children who have normal intellect may not be diagnosed with their ASD until they start school (Williams et al. 2008), when the pressures to conform to the teacher’s agenda, work in groups and establish friendships with peers are noted to be impaired. Children who present in this age group seldom have impaired acquisition of language milestones, but they do have pragmatic impairments. Such children were often previously diagnosed as having Asperger syndrome, but this is a term that has now been discontinued under DSM-5 (Rapin and Dunn 2003). In this school-age group, such pragmatic impairment may manifest itself through either difficulties in conversing, such as failing to take account of the listener’s needs, or problems understanding non-literal language such as idioms and metaphors (Hutchins et al. 2012). In addition, the child’s speech may be unusual due to abnormal prosody (McCann et al. 2007). Prosody is the suprasegmental aspect of speech that results in variations in pitch, fundamental frequency, loudness, pausing, intonation, stress and rhythm, and thus affects the meaning of what you say. It has an important function of conveying emotion, and even in able young people with ASDs it can be strikingly unusual, such that their speech sounds robotic, and can present a significant social barrier.

These pragmatic language impairments may be voiced by the referent but, alternatively, a school-aged child’s presentation can appear entirely behavioural. Comorbid conditions, such as oppositional behaviour, aggression and depression, ADHD and Gilles de la Tourette syndrome, are common (de Bruin et al. 2007a; Tuchman 2013a). These may be impair function more than the underlying ASD (Simonoff et al. 2008).

There may be poor coordination and children have often received prior diagnoses such as developmental coordination disorder (DCD), dyspraxia, benign hypotonia, hypermobility syndrome, congenital ataxia, and deficits in attention, motor control and perceptual abilities. Both ASD and DCD can present with emotional difficulties and poor social skills and children with DCD have similar difficulties recognising emotional states from facial expressions (Cummins et al. 2005). Frequently there are difficulties experienced in school as a result of poor handwriting, which can be compounded by dyslexia and difficulties with imaginary thought that affect composition. Alerting signs and symptoms of possible ASD in school-aged children and young people are shown in Table 29.6. The diagnosis of an ASD in adolescence can present particularly difficult diagnostic challenges, so it is critical to gather information from settings outside the clinic. Additional alerting signs are shown in Table 29.7. There are a number of structured questionnaires that can be completed by parents and teachers which can be very useful in this regard (Constantino 2002).

**COEXISTENCE OF ASDs WITH GENETIC AND NEUROLOGICAL DISORDERS**

**Genetic Disorders**

There is significant coexistence of the ASD phenotype with multiple genetic disorders (Zafeiriou et al. 2007; Garg et al. 2013), metabolic disorders (Zecvati and Spence 2009), neurological disorders such as Duchenne and Becker muscular dystrophy (Komoto et al. 1984; Wu et al. 2005; Hendriksen and Vles 2008, Young et al. 2008a), tuberous sclerosis (Gillberg et al. 1994; Tuchman 1994; Curatolo et al. 2004; de Vries 2008; Jeste et al. 2008), sleep disorders (Richdale 1999; Schreck et al. 2004; Oyane and Bjorvatn 2005; Allik et al. 2006; Malow et al. 2006; Goodlin-Jones et al. 2008) and epilepsy (Tuchman and Rapin 2002; Roulet-Perez and Deonna 2006; Garcia-Penas 2008; Munoz-Yunta et al. 2008) (Table 29.8).

The reported prevalence of ASDs in boys with FXS has a wide range and ASDs have been described in as many as 67%, with 90% of boys displaying at least one behaviour that is characteristic of ASDs. There also appears to be a drift towards meeting ASD criteria as children affected with FXS get older. There seems to be some evidence that social behaviours, such as avoiding group activities, not responding to joint attention and lacking empathy, along with repetitive behaviours, distinguish boys with FXS ASD from boys with just FXS. Repetitive behaviours related to stereotyped object play may be the best single predictor of ASD in boys with FXS (Brock and Hatton 2010).

Rates of ASDs in tuberous sclerosis complex vary (Jeste et al. 2014). Numis et al. (2011) described it in 40% of individuals with *TSC1* gene, more commonly with an earlier age of seizure onset and more frequent seizures. The affected individuals had EEGs with a greater amount of interictal epileptiform features in the left temporal lobe, but no difference in the regional distribution of tuber burden.
Table 29.6  Warnings of possible autistic spectrum disorders in school-age children

<table>
<thead>
<tr>
<th>Warning signs</th>
</tr>
</thead>
</table>
| Communication impairments | Abnormalities in language development including muteness  
|               | Odd or inappropriate prosody  
|               | Persistent echolalia  
|               | Reference to self as ‘you’, ‘she’ or ‘he’ beyond 3 years  
|               | Unusual vocabulary for child’s age/social group  
|               | Limited use of language for communication and/or tendency to talk freely only about specific topics  
| Social impairments | Inability to join in play of other children or inappropriate attempts at joint play (may manifest as aggressive or disruptive behaviour)  
|               | Lack of awareness of classroom ‘norms’ (criticising teachers, overt unwillingness to cooperate in classroom activities, inability to appreciate or follow current trends)  
|               | Easily overwhelmed by social and other stimulation  
|               | Showing extreme reactions to invasion of personal space and resistance to being hurried  
| Impairments of interests, activities and/or behaviours | Lack of flexible cooperative imaginative play/creativity  
|               | Difficulty in organising self in relation to unstructured space (e.g. hugging the perimeter of playgrounds, halls)  
|               | Inability to cope with change or unstructured situations, even ones that other children enjoy (school trips, teachers being away, etc.)  
| Other factors | Unusual profile of skills/deficits  
|               | Any other evidence of odd behaviours including unusual responses to sensory stimuli  

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Table 29.7  Additional warnings of possible autism spectrum disorders in adolescents

<table>
<thead>
<tr>
<th>Warning signs</th>
</tr>
</thead>
</table>
| General picture | Difficulties in social behaviours, communication and coping with change, long-standing and more obvious at times of transition  
|               | Significant discrepancy between academic ability and ‘social’ intelligence, most difficulties in unstructured social situations (e.g. in school or work breaks)  
|               | Socially ‘naive’, lacks common sense, not as independent as peers  
| Language, non-verbal skills and social communication | Problems with communication, even if wide vocabulary and normal use of grammar. May be unduly quiet, may talk at others rather than hold a to-and-fro conversation, or may provide excessive information on topics of own interest  
|               | Unable to adapt style of communication to social situations, e.g. may sound like ‘a little professor’ (overly formal), or be inappropriately familiar  
|               | May have speech peculiarities including ‘flat’, unmodulated speech, repetitiveness, use of stereotyped phrases  
|               | May take things literally and fail to understand sarcasm or metaphor  
|               | Unusual use and timing of non-verbal interaction (e.g. eye contact, gesture and facial expression)  
| Social problems | Difficulty making and maintaining peer friendships, though may find it easier with adults or younger children  
|               | Can appear unaware or uninterested in peer group ‘norms’, may alienate by behaviours that transgress ‘unwritten rules’  
|               | May lack awareness of personal space, or be intolerant of intrusions on own space  
| Rigidity in thinking and behaviour | Preference for highly specific, narrow interests or hobbies, or may enjoy collecting, numbering or listing  
|               | Strong preferences for familiar routines, may have repetitive behaviours or intrusive rituals  
|               | Problems using imagination (e.g. in writing, future planning)  
|               | May have unusual reactions to sensory stimuli (e.g. sounds, tastes, smell, touch, hot or cold)  

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Note that difficulties are likely to be more subtle in older individuals or those without intellectual disability.
Developed by the guideline group based on their knowledge of the evidence base and their clinical experience.
ASDs are observed more frequently in children with the following coexisting conditions than in the general population:

- Intellectual disability (prevalence: 8–27.9%)
- Fragile X syndrome (prevalence: 24–60%)
- Tuberous sclerosis (prevalence of ASD: 36–79%)
- Neonatal encephalopathy/infantile spasms (prevalence: 4–14%)
- Cerebral palsy (prevalence: 15%)
- Down syndrome (prevalence: 6–15%)
- Muscular dystrophy (prevalence: 3–37%)
- Neurofibromatosis (prevalence: 4–8%)

Numerous disorders with intellectual disability, an ASD and known genetic deficits have been described, and the genes of several of these syndromes have been linked to aberrant synaptic protein synthesis, suggesting a possible common pathway leading to the autism phenotype and cognitive impairment (Kelleher and Bear 2008; Jeste and Geschwind 2014). Recent evidence-based guidelines in the UK (NICE 2011) listed the frequency of coexisting medical conditions in ASD.

### Cerebral Palsy

There is considerable overlap of diagnoses between cerebral palsy and ASDs (Surén et al. 2012). ASDs have been reported in 6.9% of children with cerebral palsy overall, with 18.4% in non-spastic subtypes, particularly the hypotonic subtype. There is no increased incidence of epilepsy for children with cerebral palsy who have a comorbid ASD (Christensen et al. 2014).

### Visual Impairment

Children with a visual impairment are considered to be at greater risk of ASDs, but there is complexity to the clinical features because of the overlap in symptomatology that is common to children who are congenitally blind and those affected by an ASD. Williams et al. (2014) advise that symptoms suggestive of ASD in sighted children can be less clinically significant in children who are congenitally blind, and this includes repetitive or stereotyped finger or hand movements, repetitive interests or stereotyped behaviours, absence of pointing, limited range of facial expressions, undue sensitivity to noise, difficulty with imaginative play by parent report and difficulty establishing age-appropriate friendships. However, blind children who are congenitally visually impaired and do not have an ASD are more appropriately responsive to social situations and make appropriate social overtures. They also display shared enjoyment, as well as being able to offer comfort and direct others’ attention. Problematic maladaptive behaviours such as aggression towards family and non-family members, as well as self-injury, are often more problematic behaviours reported in blind children with an ASD than in those with uncomplicated congenital visual impairment. There have also been reports that some blind children experience a lessening of autistic symptoms after age 5, even to the extent that they no longer meet criteria for an ASD (Hobson and Lee 2010).

### Hearing Impairment

Children with ASDs have unusual listening behaviour and are insensitive to voice and language. Jure et al. (1991) demonstrated that the increase in ASDs for children with a hearing impairment can usually be explained by both conditions having a common aetiology. It has been described for individuals with congenital rubella and cytomegalovirus (CMV) (Ivarsson et al. 1990, Yamashita et al. 2003, Sweeten et al. 2004).

### PERINATAL AND NEONATAL RISK FACTORS FOR ASDs

The aetiology of ASDs is often unknown, although there is a high concordance rate in monozygotic twins of 60–92% compared with 0–10% in dizygotic twins, so genetic influences are clearly very important (Jeste and Geschwind 2014). The lack of complete concordance in monozygotic twins indicates that there is likely to be a role for environmental factors. ASD aetiology is likely to be polygenic and potentially epistatic if these environmental factors interfere with genetic factors, resulting in increased risk (Larsson et al. 2005).

The relationship between perinatal and neonatal factors and the expression of ASDs appears complex (Calderon et al. 2010, 2014). In a meta-analysis Gardner et al. (2011) reported inconsistent results, but the strongest evidence for association with ASD risk includes abnormal fetal presentations, umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal haemorrhage, summer birth, low birthweight, small for gestational age, congenital malformation, low 5-minute Apgar score, feeding difficulties, meconium aspiration, neonatal anaemia, ABO or rhesus (Rh) incompatibility and hyperbilirubinaemia. An increased risk of an ASD and associated social communication difficulties has been reported in preterm infants (Johnson et al. 2011).

CMV has been linked with a teratogenic influence affecting the migration of neural cells from the ventricular zones to the cortex during gestation. Resulting neurological disability can include ASD (Engman et al. 2010).

Maternal intake of periconceptional folic acid has been associated with a reduced ASD risk in a large population-based case–control study, with almost a 40% reduction in ASD risk. Although it is not known whether the association with an ASD is causal, there is consistency across a range of studies (Surén et al. 2013; Schmidt 2013).

A parental history of some forms of psychiatric illness confer an increased risk of ASDs in offspring. The NICE (2012) described these in parental schizophrenia, affective disorder, and other mental and behavioural disorders. Rai et al. (2013)
described an increased risk of ASDs for cases of ASDs without intellectual disability, where there was a prenatal history of maternal depression with some additional risk from antidepressant use. Rates of parental psychiatric conditions at the time of the affected infant’s birth have been described in 18.6%, incorporating schizophrenia-like psychosis, affective disorder or substance abuse (Larsson et al. 2005).

**DIAGNOSTIC TESTS FOR ASDs**

There are a variety of specialist diagnostic tools that can be used in the assessment of ASDs which are regarded as criterion standards for research. They require specialist training and can be lengthy in their administration, e.g. the Diagnostic Interview for Social and Communication Disorders (Wing et al. 2002) takes 3 hours to administer and the Autism Diagnostic Interview Revised (Lord et al. 1994), which is appropriate for children with a mental age of ≥18 months can take 1–2 hours to administer. It is generally accepted that multidisciplinary approaches to assessment and diagnosis are the criterion standard in clinical practice, with use of a number of different professionals who can employ formal assessment mechanisms and where clinical judgement remains critical, because there are no criterion standard assessments with optimum sensitivity and specificity across all age groups and complexity of development for children with a potential ASD (Samtani et al. 2011).

**INDIVIDUAL PROFILING**

**Neuropsychology**

Neuropsychological correlates include impairments in executive functioning, weak central coherence and deficits in theory of mind tasks, which look at whether the person can take on the perspective of another person (Korkman 2013). Weak central coherence is integrating information into meaningful wholes and executive functioning explores the ability to simultaneously engage in multiple tasks.

Executive functioning skills are goal-directed behaviours which include planning, working memory, multi-tasking and flexibility, and deficits can be seen in ASDs; some consider them to be related to social and non-social difficulties. Neuropsychiatric conditions are associated with executive functioning difficulties; Clark et al. (2002) have suggested that executive dysfunction can outweigh verbal intelligence as a predictor of adaptive functioning and achievement.

Children with sensory modulation disorders show intense and prolonged negative responses to everyday sounds, sights, tastes, smells, movements and touch, leading to labile emotionality and mood, with heightened stress and behaviours to avoid the input; this can be combined with maladaptive behaviour of aggression. Rates can be very high, affecting over half of children with ASD and Ben-Sasson et al. (2013) showed that high rates of sensory over-responsivity were associated with high levels of family life impairment and parenting stress, and persisted. Parents may have to compromise participation in community activities and social interactions, as well as taking avoidance procedures in activities of daily living; this was reported in the toddlers whom Ben-Sasson et al. were profiling. It has also been shown to be the case for older children with Asperger syndrome (Epstein et al. 2008). In addition, this parental stress is related to levels of executive dysfunction.

**Epileptic Seizures**

The prevalence of epileptic seizures in individuals with ASDs and intellectual disability is 21.5%, compared with 8% in those of normal intellect (Amiet et al. 2008). In the largest sample studied to date, 5815 children first diagnosed with ASDs, drawn from three genetic database populations and one epidemiological population, the two major risk factors for associated epilepsy in ASDs were IQ and age (Viscidi et al. 2013). The two major findings of this study were that the average prevalence of epilepsy in ASDs was 12%, reaching 26% by adolescence, and that one standard deviation (SD) increase in IQ decreased the odds of epilepsy by 47%. In addition, this study found that developmental regression was not a risk factor for developing epilepsy in that sample of children with a first diagnosis of ASD.

Multiple studies on regression and epilepsy have demonstrated that there is no increase in epileptic seizures associated with the preschool regression seen in ASDs (Shinnar et al. 2001, Valicenti-McDermott et al. 2008). The timing of the regression and the features of the language impairment are important considerations to orient the clinician to the possibility of ASDs as opposed to other conditions associated with loss of speech (Korkman et al. 1998; Tagawa et al. 1999; Wheless et al. 2002; McVicar et al. 2005; Trevathan 2005; Gallagher et al. 2006).

ASDs and epilepsy share genetic variants and pathophysiological mechanisms such as dysregulation of excitation/inhibition imbalance, caused by defects in either GABAergic fibres or γ-aminobutyric acid (GABA)-receptor function (Jeste and Tuchman 2015). Children with epilepsy are at high risk for developing ASDs and social cognitive impairments (Tuchman 2013b). In a large community-based cohort of childhood onset epilepsy (n=555) followed prospectively, 30% of children with infantile spasms and intellectual disability had a diagnosis of ASD (Berg et al. 2011). The bidirectionality of the ASD–epilepsy relationship suggests that there should be a high degree of vigilance for epilepsy in children with ASDs, and for ASDs and social cognitive impairments in children with epilepsy.

The complex relationship between epilepsy and ASD has recently been extensively reviewed (Tuchman et al. 2010a, b).

**Clinical Features (Physical)**

There are certain physical features to pay attention to over and above the behavioural features that may assist in establishing...
Consider the following differential diagnoses for ASDs (see corresponding chapters) and whether specific assessments are needed to help interpret the ASD history and observations:

### Neurodevelopmental disorders
- Specific language delay or disorder
- Intellectual disability or global developmental delay
- Developmental coordination disorder (DCD)

### Mental and behavioural disorders
- Attention-deficit–hyperactivity disorder (ADHD)
- Mood disorder
- Anxiety disorder
- Attachment disorders
- Oppositional defiant disorder (ODD)
- Conduct disorder
- Obsessive–compulsive disorder (OCD)
- Psychosis

### Conditions in which there is developmental regression
- Rett syndrome
- Epileptic encephalopathy

### Other conditions
- Severe hearing impairment
- Severe visual impairment
- Maltreatment
- Selective mutism

---

The range of investigations for establishing an underlying aetiology for ASD is extremely wide; it must be informed by the presenting history and physical examination, with a particular note of any dysmorphic features. The heterogeneous aetiologies of non-genetic ASDs require tailored investigations, for example, exploration of an intrauterine CMV infection (see Chapter 2). A hearing test must always be performed, but potentially the most helpful investigations are genetic.

### Genetic Testing

Advances in genetic technology can now result in a diagnostic yield of aetiology in ASDs of 30–40%. Table 29.10 summarises the ASD genotypes with their phenotypes.

This yield is likely to increase even more with next-generation sequencing (Jeste and Geschwind 2014). An empirical recurrence risk in individuals without an identifiable aetiology is 3–10%. There is some modification for sex so risk is 7% if the child is a girl and 4% if the child is a boy, but if there are multiple children already affected with ASDs then there is a 30% recurrence risk (Schaefer et al. 2013). Rosti et al. (2014) argue that a good starting point to consider genetics is to distinguish between the ASD without an identifiable aetiology, for which the phrase ‘essential’ ASD is coined; such cases make up about 75%. These are children who lack dysmorphic features, have a high male:female ratio, a higher sibling recurrence rate and a positive family history. The sibling recurrence rate is up to 35% and a positive family history of up to 20%. Rosti et al. (2014) propose that a ‘syndromic’ ASD, that is, one that is characterised by accompanying recognisable patterns of dysmorphism, a reduced male:female ratio (3.5:1), a lower recurrence risk (4–6%) and a family history, occurs to a lesser extent (up to 9%). They propose that single gene disorders are mainly metabolic conditions that have accompanying ASD features (Table 29.11).

Schaefer et al. (2013) suggest a first- and second-tier investigation approach for the genetic investigations for individuals with ASDs (Table 29.12).

Rett syndrome and examination of mutations in the MECP2 gene need to be considered for girls who present with

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**Table 29.10** Differential diagnosis for autism spectrum disorders (ASDs)

<table>
<thead>
<tr>
<th>Differential diagnosis for autism spectrum disorders (ASDs)</th>
<th>Table 29.10</th>
</tr>
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<tbody>
<tr>
<td>Consider the following differential diagnoses for ASDs</td>
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<tr>
<td>(see corresponding chapters) and whether specific assessments</td>
<td></td>
</tr>
<tr>
<td>are needed to help interpret the ASD history and observations:</td>
<td></td>
</tr>
<tr>
<td>Neurodevelopmental disorders</td>
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<tr>
<td>Developmental coordination disorder (DCD)</td>
<td></td>
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<tr>
<td>Mental and behavioural disorders</td>
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<tr>
<td>Attention-deficit–hyperactivity disorder (ADHD)</td>
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<tr>
<td>Mood disorder</td>
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<td>Anxiety disorder</td>
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<tr>
<td>Attachment disorders</td>
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<tr>
<td>Oppositional defiant disorder (ODD)</td>
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<tr>
<td>Conduct disorder</td>
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<tr>
<td>Obsessive–compulsive disorder (OCD)</td>
<td></td>
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<tr>
<td>Psychosis</td>
<td></td>
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<tr>
<td>Conditions in which there is developmental regression</td>
<td>Rett syndrome</td>
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<tr>
<td>Rett syndrome</td>
<td>Epileptic encephalopathy</td>
</tr>
<tr>
<td>Other conditions</td>
<td>Severe hearing impairment</td>
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<tr>
<td>Severe hearing impairment</td>
<td>Severe visual impairment</td>
</tr>
<tr>
<td>Maltreatment</td>
<td>Selective mutism</td>
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</tbody>
</table>

Reproduced with permission from the National Institute for Health and Care Excellence (2011).
ASDs. When individuals with Rett syndrome with an earlier diagnosis of ASD are compared with those with a first diagnosis of Rett syndrome, the differences tend to reflect the fact that there is better preservation of speech in the former, with less involvement of hand use and more persistence of ambulation. Most MECP2 mutations will be identified on whole-exome/whole-genome sequencing, and 17.6% of patients with MECP2-positive Rett syndrome have an earlier diagnosis of ASDs (Young et al. 2008b). MECP2 mutations have been linked to a range of clinical phenotypes beyond ASDs. A novel A140V MECP2 mutation was identified in a 12-year-old girl who had experienced some earlier difficulty socialising with her peer group, showed a preference from early school age for routine and had severe non-verbal learning disability. She became increasingly withdrawn and then disinhibited with obsessive–compulsive behaviour, and received a diagnosis at

<table>
<thead>
<tr>
<th>ASD-related genotype</th>
<th>Epilepsy</th>
<th>Dysmorphism</th>
<th>Intellectual disability</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21.1 deletion syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Schizophrenia, CHA, cataracts, limb/hand abnormalities</td>
</tr>
<tr>
<td>1q21.1 duplication syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Macrocephaly, schizophrenia</td>
</tr>
<tr>
<td>2q37 deletion syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Moderate to severe</td>
<td>Pain insensitivity, brachydactyly</td>
</tr>
<tr>
<td>3q29 deletion syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Severe schizophrenia</td>
</tr>
<tr>
<td>3q29 duplication syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Excessive hand creases, pes planus</td>
</tr>
<tr>
<td>13q14 deletion syndrome</td>
<td>−</td>
<td>Facial</td>
<td>Mild to severe</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>15q13.3 deletion syndrome</td>
<td>Genetic generalised</td>
<td>Mild facial</td>
<td>Mild to severe</td>
<td>Dyspraxia and dysarticulation, skeletal/hand abnormalities</td>
</tr>
<tr>
<td>15q11-q13 duplication syndrome</td>
<td>+</td>
<td>−</td>
<td>Moderate to severe</td>
<td>Ataxia, hypotonia, sudden unexpected death</td>
</tr>
<tr>
<td>16p11.2 deletion syndrome</td>
<td>+</td>
<td>Variable, systemic</td>
<td>Moderate to severe</td>
<td>Obesity</td>
</tr>
<tr>
<td>16p11.2 duplication syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Microcephaly, attention-deficit–hyperactivity disorder</td>
</tr>
<tr>
<td>16p12.1 deletion syndrome</td>
<td>+</td>
<td>Facial</td>
<td>Mild to moderate</td>
<td>CHA and skeletal abnormalities</td>
</tr>
<tr>
<td>17q12 deletion syndrome</td>
<td>+</td>
<td>Variable, systemic</td>
<td>Mild to moderate</td>
<td>Schizophrenia, maturity-onset diabetes of young people</td>
</tr>
<tr>
<td>17q21.31 deletion syndrome</td>
<td>+</td>
<td>Variable, systemic</td>
<td>Mild to severe</td>
<td>Severe hypotonia, friendly demeanour</td>
</tr>
<tr>
<td>17q21.31 duplication syndrome</td>
<td>−</td>
<td>Mild facial</td>
<td>Mild to moderate</td>
<td>Microcephaly, hirsuitism, limb/hand abnormalities, atopic dermatitis</td>
</tr>
<tr>
<td>BCKDK</td>
<td>+</td>
<td>−</td>
<td>Mild to moderate</td>
<td>Low plasma branched-chain amino acids</td>
</tr>
<tr>
<td>CACNA1C</td>
<td>−</td>
<td>Webbing of fingers and toes, no hair at birth</td>
<td>Mild to moderate</td>
<td>Long Q–T syndrome</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>Focal</td>
<td>−</td>
<td>Mild to moderate</td>
<td>Features of Gilles de la Tourette syndrome</td>
</tr>
<tr>
<td>FOXP2</td>
<td>−</td>
<td>−</td>
<td>Mild to moderate</td>
<td>Verbal dyspraxia</td>
</tr>
<tr>
<td>MECP2 dup (males)</td>
<td>−</td>
<td>−</td>
<td>Severe</td>
<td>Recurrent respiratory infections</td>
</tr>
<tr>
<td>NLGN4 (males)</td>
<td>−</td>
<td>−</td>
<td>Moderate to none</td>
<td>Depression, anxiety and intellectual disability in females</td>
</tr>
<tr>
<td>NRXN1</td>
<td>+</td>
<td>Facial</td>
<td>Mild to moderate</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>PTEN</td>
<td>−</td>
<td>Facial</td>
<td>Mild to moderate</td>
<td>Macrocephaly</td>
</tr>
<tr>
<td>SHANK1 (males)</td>
<td>−</td>
<td>−</td>
<td>None</td>
<td>Reduced penetrance in females</td>
</tr>
<tr>
<td>SHANK2</td>
<td>−</td>
<td>−</td>
<td>Mild to moderate</td>
<td></td>
</tr>
<tr>
<td>SHANK3</td>
<td>−</td>
<td>Mild facial</td>
<td>Moderate to severe</td>
<td>Essentially non-verbal</td>
</tr>
<tr>
<td>SLC6A8 (males)</td>
<td>+</td>
<td>Facial</td>
<td>Severe</td>
<td>Megacolon, ileus</td>
</tr>
<tr>
<td>TMLHE (males)</td>
<td>±</td>
<td>−</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

From Rosti et al. (2014). CHA, congenital heart abnormalities.
the age of 12 of bipolar disorder. She was noted to have some parkinsonian features, along with these severe psychiatric symptoms, and some cognitive regression (Venkates-Waran et al. 2014).

Role of Cranial Imaging

Cranial imaging may be indicated as part of the assessment of an accompanying learning disability, but is not indicated as such in the investigation of the aetiology of the ASD. There is a lack of definitive data with respect to the role of imaging in elucidating the neurobiology of ASDs (Volkmar et al. 2014). However, the limbic system appears to be involved from some postmortem studies and functional magnetic resonance imaging (fMRI) has identified difficulties during tasks of social and affective judgement, and processing of facial and non-facial stimuli. Structural MRI shows that the brain size is increased in ASDs and diffusion tensor imaging suggests that aberrations in development of the white matter track occur. However, this information remains at the research level and does not support cranial imaging in everyday aetiological investigation for ASDs.

Additional Investigations

Investigation for iron deficiency anaemia, nutritional deficiencies and lead levels needs to be judged on an individual basis. Children with ASDs can have complex restrictive diets and amino acid deficiencies; lower bone density has been described against age-matched control groups (Arnold et al. 2003; Hediger et al. 2008; Keen 2008) and there are differences in nutritional intakes (Hyman et al. 2012). However, reports differ. Emond et al. (2010) reported no difference in energy intake or growth for children with ASDs.

### Table 29.11 Recently described metabolic conditions associated with an autism spectrum disorder phenotype

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
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<tbody>
<tr>
<td>3β-hydroxycholesterol-7-reductase deficiency</td>
</tr>
<tr>
<td>(Smith–Lemli–Opitz syndrome)</td>
</tr>
<tr>
<td>6-N-trimethyl-lysine dioxygenase deficiency</td>
</tr>
<tr>
<td>Adenylsuccinate lyase deficiency</td>
</tr>
<tr>
<td>Cerebral folate deficiency</td>
</tr>
<tr>
<td>Cytosolic 5′-nucleotidase superactivity</td>
</tr>
<tr>
<td>Dihydropyrimidinase deficiency</td>
</tr>
<tr>
<td>Disoders of creatinine transport or metabolism</td>
</tr>
<tr>
<td>Disorders of γ-aminobutyric acid metabolism</td>
</tr>
<tr>
<td>Phosphoribosylpyrophosphate synthetase superactivity</td>
</tr>
<tr>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
</tr>
<tr>
<td>Sulfation defects</td>
</tr>
</tbody>
</table>

Reproduced from Schaeffer et al. (2013), with permission of Macmillan Publishers Ltd. © 2013.

### INTERVENTIONS

Most interventions in ASDs are evaluated against outcomes such as cognition, language or amelioration of maladaptive behaviours, rather than by quality of life. There are particular challenges to assessing quality of life in ASDs because the children may not have the language skills to express their views, or they may have difficulty identifying, discriminating and describing their emotional state. However, several possible indicators of quality of life in ASD, such as social support, academic functioning or satisfactory employment, family life and self-determination, are all important to keep in mind when advising parents (Burgess and Gutstein 2007).

This is particularly the case if the clinician is considering pharmacological treatments because these can be effective, but they have only a limited role in addressing particular symptoms and should be considered only after careful deliberation of the risks and benefits (Volkmar et al. 2014). They are generally considered for the treatment of comorbid psychiatric or neurodevelopmental conditions in ASDs, and are usually a short- to medium-term intervention. Pharmacological treatments by or in collaboration with clinicians who have appropriate training and experience include risperidone for the short-term treatment of significant aggression, methylphenidate for the treatment of attention difficulties and hyperactivity, and melatonin for the treatment of intractable sleep problems (Braam et al. 2009). A summary of the evidence for efficacy and significant side effects is shown in Table 29.13.

Children with ASDs have less total sleep duration, which includes more frequent waking at night time; this is evident from 30 months of age and persists until adolescence. This decrease in sleep duration does not appear to be entirely accounted for by the increased sleep disturbance seen for children with a learning disability. It is possible that it has a relationship to reduced behaviour and family distress in the day time. There is increasing evidence that the fundamental differences in circadian melatonin production for some children with ASDs can reduce sleep latency, so melatonin can increase the sleep duration for children with ASDs (Humphreys et al. 2014).

There is a substantive literature on the neuropsychological underpinnings of symptoms, signs and surface behaviours in ASDs, and these have made a substantial contribution to informing interventions. There is a whole range of examples that incorporate a wide range of psychosocial interventions, most of which are based on behavioural theory or communication-focused therapies (Seida et al. 2009). Many of the studies had methodological weaknesses, but the overall picture was of a positive outcome, with an impression that some form of treatment was more favourable than no treatment at all. Neuropsychological insights might allow for treatment to be adapted for children with ASDs such as cognitive–behavioural therapy for anxiety, where the impairments of social skills, self-care, organisational skills, and circumscribed interests and stereotypies can be accommodated in the way that the therapy is applied (Wood et al. 2009; Ung et al. 2015).
Similarly, neuropsychological insights have informed interventions for very young children, such as targeting joint attention behaviour for infants (Whalen and Schreibman 2003; Warreyn et al. 2014), and have provided the impetus to identify the condition as early as possible in high-risk populations. Sometimes well-established neuropsychological understanding, such as that of ‘mentalising’, that is, the ability to impute the thoughts of others (Fisher and Happe 2005; O’Hare et al. 2009), may still be under development in terms of an evidence base for efficacy, but they do inform how a child’s environment might be potentially modified to support his or her difficulties (Thieumann and Goldstein 2001; Wellman et al. 2002). Information about the early impairments in ASDs also informs approaches in parent-mediated programmes (Green et al. 2010).

It is of course critical to pursue evidence bases for interventions for very young children, such as targeting joint attention behaviour for infants (Whalen and Schreibman 2003; Warreyn et al. 2014), and have provided the impetus to identify the condition as early as possible in high-risk populations. Sometimes well-established neuropsychological understanding, such as that of ‘mentalising’, that is, the ability to impute the thoughts of others (Fisher and Happe 2005; O’Hare et al. 2009), may still be under development in terms of an evidence base for efficacy, but they do inform how a child’s environment might be potentially modified to support his or her difficulties (Thieumann and Goldstein 2001; Wellman et al. 2002). Information about the early impairments in ASDs also informs approaches in parent-mediated programmes (Green et al. 2010).

Communication is a major focus of intervention, and alternative communication modalities such as sign language, visual supports and picture exchange may be indicated. Programmes to enhance social reciprocity and pragmatic language skills may be appropriate. Structured educational models can show some efficacy such as the Early Start Denver Model (Dawson et al. 2010) and the Treatment and Education of Autism and Related Communication Handicapped Children’s Programme (Schopler 1994). These are reviewed in in the 2014 review ‘Practice parameters for assessment and treatment of children and adolescents with autism spectrum disorder’ (Volkmar et al. 2014).

Although there are a number of other techniques working on sensory modulation difficulties and trying to help through social pragmatic models of intervention, a clear evidence base for their efficacy can be outstanding (Volkmar et al. 2014).

Sensory modulation difficulties are prevalent in ASDs. In addition to addressing areas of need in activities of daily living, executive function, handwriting and other motor skills, occupational therapy is often considered in order to promote the ability of the child with an ASD to manage sensory processing. There are two main approaches including sensory integration therapy, which is child centred and usually clinic based, and sensory-based intervention, which employs environmental modification. The evidence base for both approaches is presently insufficient to advocate one over the other (Lang et al. 2012; Case-Smith et al. 2014).

**PROGNOSIS**

There are a number of broad indicators to prognosis; children may do better than these historical groups if their condition is...
<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Target symptoms</th>
<th>Dose</th>
<th>Demographics</th>
<th>Significant side effects</th>
<th>Primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α₂-Agonists</strong></td>
<td></td>
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</tr>
<tr>
<td>Clonidine</td>
<td>Jaselskis et al. (1992)</td>
<td>Hyperactivity, irritability, inappropriate speech, stereotypy</td>
<td>0.15–0.20mg divided 3×/day</td>
<td>8 children 5–13 years</td>
<td>Hypotension, drowsiness</td>
<td>Statistically and clinically relevant decrease in ABC irritability subscale</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Handen et al. (2008)</td>
<td>Hyperactivity, inattention</td>
<td>1–3mg divided 3×/day</td>
<td>7 children with ASD 5–9 years</td>
<td>Drowsiness, irritability</td>
<td>45% with &gt;50% decrease in ABC hyperactivity subscale</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td>Marcus et al. (2009)</td>
<td>Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech</td>
<td>5, 10 or 15mg/day fixed dose</td>
<td>218 children 6–17 years</td>
<td>Somnolence, weight gain, drooling, tremor, fatigue, vomiting</td>
<td>56% positive response for aripiprazole 5mg vs 35% on placebo; significant improvement in irritability, hyperactivity and stereotypy subscals</td>
</tr>
<tr>
<td></td>
<td>Owen et al. (2009)</td>
<td>Irritability, hyperactivity, stereotypy, social withdrawal inappropriate speech</td>
<td>5–15mg/day flexibly dosed</td>
<td>98 children 6–17 years</td>
<td>Somnolence, weight gain, drooling, tremor, fatigue, vomiting</td>
<td>52% positive response for aripiprazole vs 14% on placebo; significant improvement in Irritability, hyperactivity, and stereotypy subscals</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Anderson et al. (1984)</td>
<td>Multiple behavioural symptoms, global functioning</td>
<td>0.5–4.0mg/day</td>
<td>40 children 2–7 years</td>
<td>Sedation, irritability, extrapyramidal symptoms (≥25%)</td>
<td>Behavioural symptoms improved with significant decrease in 8 of 14 items of CPRS</td>
</tr>
<tr>
<td></td>
<td>Anderson et al. (1989)</td>
<td>Multiple behavioural symptoms, global functioning</td>
<td>0.25–4mg/day</td>
<td>45 children 2–7 years</td>
<td>Sedation, extrapyramidal symptoms</td>
<td>Behavioural symptoms improved with significant decrease in 7 of 14 items of CPRS</td>
</tr>
<tr>
<td></td>
<td>Hollander et al. (2006)</td>
<td>Global functioning, aggression, compulsions, irritability</td>
<td>7.5–12.5mg/day</td>
<td>11 children 6–14 years</td>
<td>Weight gain, sedation</td>
<td>50% of those on olanzapine much or very much improved in global functioning vs 20% on placebo</td>
</tr>
<tr>
<td>Risperidone</td>
<td>RUPP (2002)</td>
<td>Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech</td>
<td>0.5–3.5mg/day</td>
<td>101 children 5–17 years</td>
<td>Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness</td>
<td>69% had positive response for risperidone vs 12% positive response on placebo; significant positive findings for hyperactivity and stereotypy</td>
</tr>
<tr>
<td></td>
<td>Shea et al. (2004)</td>
<td>Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech</td>
<td>0.02–0.06mg/kg per day</td>
<td>79 children 5–12 years</td>
<td>Weight gain, somnolence</td>
<td>64% improvement in ABC Irritability subscale on risperidone vs 31% improvement on placebo; significant positive finding for hyperactivity</td>
</tr>
<tr>
<td></td>
<td>McDougle et al. (2005)</td>
<td>Social and communication impairment, repetitive behaviour and stereotypy</td>
<td>0.5–3.5mg/day</td>
<td>101 children 5–17 years</td>
<td>Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness</td>
<td>Significant response for repetitive behaviour and stereotypy on risperidone</td>
</tr>
<tr>
<td><strong>Mood stabilisers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Hellings et al. (2005)</td>
<td>Irritability</td>
<td>20mg/kg per day, average level 75–78</td>
<td>30 subjects 6–20 years</td>
<td>Increased appetite, skin rash</td>
<td>No significant difference for ABC Irritability subscale</td>
</tr>
<tr>
<td></td>
<td>Hollander et al. (2005)</td>
<td>Repetitive behaviour</td>
<td>500–1500mg/day</td>
<td>12 children 5–17 years, 1 adult 40 years</td>
<td>Irritability, aggression</td>
<td>Statistically significant decrease in repetitive behaviour on CY-BOCS</td>
</tr>
<tr>
<td></td>
<td>Hollander et al. (2010)</td>
<td>Global irritability</td>
<td>Dosed to mean level of 89.8mg/mL</td>
<td>27 children 5–17 years</td>
<td>Skin rash, irritability</td>
<td>62.5% positive response for irritability on CGI on divalproex vs 9.09% on placebo</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Target symptoms</th>
<th>Dose</th>
<th>Demographics</th>
<th>Significant side effects</th>
<th>Primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Belsito et al. (2001)</td>
<td>Irritability, social behaviour</td>
<td>5mg/kg per day</td>
<td>28 children 3–11 years</td>
<td>Insomnia, hyperactivity</td>
<td>No significant difference in irritability or social behaviour on multiple instruments</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Wasserman et al. (2006)</td>
<td>Irritability, global functioning</td>
<td>20–30mg/kg per day</td>
<td>20 children 5–17 years</td>
<td>Aggression</td>
<td>No significant difference in global functioning or irritability</td>
</tr>
<tr>
<td>Noradrenaline reuptake inhibitors</td>
<td>Harferkamp et al. (2012)</td>
<td>Hyperactivity, inattention</td>
<td>1.2mg/kg per day</td>
<td>97 children 6–17 years</td>
<td>Nausea, anorexia, fatigue, early wakening</td>
<td>Significant difference in the ADHD-RS for active treatment group; no difference in CGI-I</td>
</tr>
<tr>
<td>Atomoxetine HCI</td>
<td>Arnold et al. (2006)</td>
<td>Hyperactivity, inattention</td>
<td>20–100mg divided 2, mean 44mg/day</td>
<td>16 children 5–15 years</td>
<td>Upper GI symptoms, fatigue, racing heart</td>
<td>57% positive response for parent-rated ABC Hyperactivity subscale vs 25% on placebo</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>King et al. (2009)</td>
<td>Repetitive behaviour</td>
<td>2.5–20mg/day, mean 9.9mg/day</td>
<td>149 children 5–17 years</td>
<td>None significant</td>
<td>Statistically significant decrease in repetitive behaviour on CY-BOCS compulsions scale</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Hollander et al. (2005)</td>
<td>Repetitive behaviour</td>
<td>2.4–20mg/day, mean 9.9mg/day</td>
<td>39 children 5–17 years</td>
<td>Decreased appetite, insomnia, irritability, emotionality</td>
<td>No significant difference in repetitive behaviour on CPRS</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Gordon et al. (1993)</td>
<td>Stereotypy, repetitive behaviour, compulsions</td>
<td>25–250mg/day, mean 15.2mg/day</td>
<td>12 children 6–18 years</td>
<td>Insomnia, constipation, twitching, tremors</td>
<td>Decrease in repetitive behaviour on CPRS</td>
</tr>
<tr>
<td>Remington et al. (2001)</td>
<td>Stereotypy, irritability, hyperactivity</td>
<td>100–150mg/day, mean 128.4</td>
<td>&lt;20 subjects</td>
<td>No significant difference in stereotypy, irritability, or hyperactivity for clomipramine on ABC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>RUPP (2005)</td>
<td>Hyperactivity</td>
<td>7.5–50mg/day divided 3/day</td>
<td>58 children 5–14 years</td>
<td>Decreased appetite, insomnia, irritability, emotionality</td>
<td>49% positive responders for hyperactivity vs 15.5% on placebo</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Pearson et al. (2013)</td>
<td>Hyperactivity, inattention</td>
<td>10–40mg each morning, methylphenidate extended release</td>
<td>24 children 7–12 years</td>
<td>Decreased appetite, insomnia</td>
<td>Significant decrease in hyperactivity and inattention on multiple teacher and parent measurements</td>
</tr>
<tr>
<td>Handen et al. (2000)</td>
<td>Hyperactivity</td>
<td>0.3–0.6mg/kg per dose, 2–3/day</td>
<td>13 children 5–11 years</td>
<td>Social withdrawal, irritability</td>
<td>8 of 13 children with &gt;50% decrease in hyperactivity on Teacher Conners hyperactivity subscale</td>
<td></td>
</tr>
<tr>
<td>Quintana et al. (1995)</td>
<td>Hyperactivity</td>
<td>10–20mg 2/day</td>
<td>10 children 7–11 years</td>
<td>Irritability, anorexia, insomnia</td>
<td>Decrease in ABC hyperactivity subscale by 8 points over placebo</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>Study</td>
<td>Target symptoms</td>
<td>Dose</td>
<td>Demographics</td>
<td>Significant side effects</td>
<td>Primary outcome(s)</td>
</tr>
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<td>-----------------------------------</td>
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</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>‘King et al. (2001)’</td>
<td>Hyperactivity, irritability</td>
<td>2.5–5.0mg/kg per day</td>
<td>39 children 5–19 years</td>
<td>Insomnia</td>
<td>No statistical difference in parent ABC hyperactivity or irritability subscales, statistical improvement in clinician hyperactivity and inappropriate speech subscales</td>
</tr>
<tr>
<td>Cyproheptadine (in combination with haloperidol)</td>
<td>Akhoundzadeh et al. (2004)</td>
<td>ABC total score, CARS</td>
<td>Titrated up to 0.2mg/kg/day</td>
<td>40 children 3–11 years</td>
<td>None significant, trend toward increased appetite</td>
<td>Statistically significant difference in ABC total score and CARS diagnostic screening tool, with unknown clinical significance</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Chez et al. (2003)</td>
<td>‘Autistic behavior,’ expressive-receptive communication</td>
<td>1.25–2.5mg/day</td>
<td>43 children 2–10 years</td>
<td>Diarrhea, stomach cramping, irritability</td>
<td>‘Autistic behavior’ statistically, improved on CARS diagnostic screening tool with unknown clinical significance</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Willemsen-Swinkels et al. (1995)</td>
<td>‘Social behavior,’ irritability</td>
<td>Single 40-mg dose</td>
<td>20 children 3–7 years</td>
<td>Sedation, increased stereotypy</td>
<td>No effect on social behavior; significant decrease on ABC Irritability subscale vs placebo</td>
</tr>
<tr>
<td></td>
<td>‘Kolmen et al. (1995)’</td>
<td>Hyperactivity, communication initiation</td>
<td>1mg/kg/day</td>
<td>13 children 3–8 years</td>
<td>Transient sedation</td>
<td>No significant difference in communication initiation</td>
</tr>
<tr>
<td></td>
<td>‘Feldman et al. (1999)’</td>
<td>Communication</td>
<td>1mg/kg/day</td>
<td>24 children 3–8 years</td>
<td>Transient sedation</td>
<td>No significant difference in multiple communication measurements</td>
</tr>
<tr>
<td>Campbell et al. (1993)</td>
<td>CGI, CPRS, discriminant learning, hyperactivity</td>
<td>0.5–1mg/kg/day</td>
<td>18 children 3–8 years</td>
<td>Increased aggression and stereotypy</td>
<td>No significant difference on CGI or CPRS or discriminant learning; positive trend for hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Campbell et al. (1990)</td>
<td>Hyperactivity, discriminant learning, self-injurious behaviour</td>
<td>0.5–1mg/kg/day</td>
<td>41 children 3–8 years</td>
<td>None significant</td>
<td>Significantly decreased hyperactivity; no effect on discriminant learning; positive trend for self-injurious behaviour</td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline (in combination with risperidone)</td>
<td>Akhoundzadeh et al. (2010)</td>
<td>Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech</td>
<td>200–600mg/day</td>
<td>40 children 4–12 years</td>
<td>Sedation, GI effects, increased appetite</td>
<td>Significant improvement on ABC Irritability and Social Withdrawal subscales</td>
</tr>
</tbody>
</table>


*A positive response in this study was defined as a greater than 25% decrease in ABC (CY-BOCS) compulsions score and a much improved or very much improved rating on the CGI-I.

For details of the references cited in the column Study and the scales used, please consult the original paper.

Note: ABC, Autism Behavior Checklist; ADHD-RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; CY-BOCS, Children’s Yale-Brown Obsessive Compulsive Scale; CARS, Childhood Autism Rating Scale; CPRS, Children’s Psychiatric Rating Scale; EPS, extrapyramidal side effects; GI, gastrointestinal; PDD, pervasive developmental disorder; RUPP, Research Units on Pediatric Psychopharmacology.

*A positive response in this study was defined as a >25% reduction in the ABC subscale and a Much Improved or Very Much Improved rating on the Clinical Global Impression–Global Improvement (CGH).

‘Study identified as funded by pharmaceutical industry.
recognised early and they have early intervention (Pickles et al. 2016). Prognosis can also be affected by the underlying syndromic explanation for an ASD, if one exists. Thus, discussion of prognosis is complex and one may not be in a position to predict too far ahead at the time of early diagnosis, although it is important to remember that parents value good quality information and also an opportunity to ask questions during the disclosure of their child’s diagnosis.

Anderson et al. (2014) reported a longitudinal study of individuals diagnosed with ASDs at age 2 years, who were followed up until age 19. They reported that 9% of these adolescents, who had had an intellectual assessment in the normal range at age 2, no longer met criteria for a clinical diagnosis of an ASD. In addition, there were 28% without intellectual disabilities who, although still having some degree of social impairment, were performing at an age-appropriate level in their cognitive and academic functioning. They found that this pattern of progress was quite slow to evolve in the sense that, even at the age of 9, the children still met criteria for an ASD, and they suggested that one needs to follow individuals into adult life to identify those who were going to have this very positive outcome conclusively. The converse of this research is that individuals with an identified intellectual disability at age 2 years had a much poorer prognosis and continued to meet criteria for ASDs in young adult life. Infant and toddler oral and motor manual skills in ASDs also correlate with later speech fluency (Gernsbacher et al. 2008).

Individual profiling for cognitive functioning in young children with ASDs may be valuable in terms of informing prognosis (Howlin et al. 2014). Severe language delay in childhood with no speech by age 5 years is associated with a poor outcome, as is the addition of epilepsy. Individuals with an IQ in the average range tend to maintain this when reassessed in middle adult life. The outlook for an individual living independently in adult life is much reduced if they had an IQ <70 in childhood and poor language development (Howlin et al. 2004).

Language outcome in adolescence may be similar for those with and those without language loss, but nevertheless it is poorer than the outcome that might otherwise have been expected for children who had earlier language acquisition before the onset of their regression (Pickles et al. 2009). Quality of social engagement with peers is important for prognosis, and a better functioning and ultimately improved quality of life for individuals affected by ASDs is predicted by their skills in this area, rather than their cognitive functioning and academic achievements (McGovern and Sigman 2005). Prognosis is not more adversely affected in children who have presented with an earlier history of regression and, generally speaking, this dramatic regression in infancy is not repeated in later life, although a more insidious form of regression has been described in adolescence (Billstedt et al. 2005), and there has been the very rare but dramatic presentation described of onset catatonia in adult life (Wing and Shah 2000).

Close et al. (2012) reported that specific co-occurring conditions could lead to a change in an ASD diagnosis, so that, on follow-up some years later, it was no longer current. The stability of the ASD diagnosis was much increased by the presence of intellectual disability and epilepsy, whereas it was decreased by the presence of a past hearing problem, and affected similarly by the presence of depression and behavioural and conduct problems. Delayed speech and speech problems in an intellectual disability, along with anxiety, were more likely to lead to persistence of the diagnosis. ADHD caused some change in diagnosis away from an ASD for some individuals.

Rates of epilepsy range from 1.8% to 23.7% and are generally similar to those reported in general populations of individuals with intellectual disability (Woolfenden et al. 2012a). The standard mortality rates for individuals with ASDs is two to three times higher than peers, but similar to populations with an intellectual disability alone, and epilepsy was responsible for 7–30% of these deaths (Woolfenden et al. 2012a).

SIGNPOSTING INDIVIDUALS AND FAMILIES TO INFORMATION ON ASDs

Affected individuals, where appropriate, and their families may also benefit from interventions to inform them about ASDs and to help them build up their own skills, such as in parenting their affected child. Children, young people and their families can be encouraged to continue to learn about ASDs through interventions and support and there is a range of sources of further information appended in recent guidelines (SIGN 2016).

The literature from the charity Research Autism (www.researchautism.net) urges the professional to ‘recognise the value of people with ASD and the contribution they can make to society, without minimising the difficulties they and their families face’. Young people have voiced that they want to be told the truth about their ASD condition and that they found the diagnosis supportive; they expressed a preference that their peers know about the kinds of difficulties that they experienced and what might help them (SIGN 2007).

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Chapter 30

Attention-Deficit–Hyperactivity Disorder and Co-existing Impairments

Bruce K Shapiro

Attention-deficit–hyperactivity disorder (ADHD) is a neurological disorder that is manifest through behavioural symptomatology and defined by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity. It became a diagnosis in the revised edition of the third DSM-III-R (APA 1987) and built upon the previous diagnoses of attention deficit disorder (ADD), minimal brain dysfunction (MBD) and hyperkinetic reaction disorder of childhood. ADHD remains a construct that is still evolving as evidenced by the recent changes in DSM-5 (APA 2013).

Perhaps the most significant change in DSM-5 is the decision to classify ADHD as a neurodevelopmental disorder and not include it with the Disruptive, Impulse Control and Conduct Disorders. This change separates ADHD from oppositional defiant disorder and conduct disorder and expands the focus to functional impairments. Classifying ADHD as a neurodevelopmental disorder will emphasise the possibility of co-existing disorders and may lead to more comprehensive assessment across multiple domains of function. The end result being faster access to the full complement of therapeutic interventions for the full array of impairments associated with ADHD (Tannock 2013).

The symptoms listed for ADHD were originally designed for school-aged children. Since DSM-IV it has become clear that ADHD precedes school and extends into adulthood. The DSM-V has made changes that attempt to address older adolescents and adults. The number of symptoms of inattention and/or hyperactivity/impulsivity required for diagnosis in older adolescents and adults have been decreased from six or more, to at least five symptoms. While the questions have not changed, explanatory examples that are appropriate to older adolescents and adults are included. This may lead to increased recognition of ADHD in older populations and a resultant increase in prevalence. DSM-5 did not include changes that would modify the diagnosis in preschool children and infants.

Another substantial change is the removal of subtypes of ADHD and replacing them with specifiers of current function. This was done because the DSM-IV classification did not identify discrete subgroups with long-term stability (Tannock 2013). Other changes include removing pervasive developmental disorder and autism as exclusionary conditions, increasing the age at onset to 12 years from 7, and explicitly requiring information from at least two different informants.

The other major classification system, ICD-10 (WHO 1992) uses symptoms that mirror the DSM. The ICD lists nine symptoms of inattention, five symptoms of hyperactivity and four symptoms of impulsivity. To make the diagnosis of hyperkinetic disorder requires at least six symptoms of inattention, at least three symptoms of hyperactivity and at least one symptom of impulsivity. Inattention, hyperactivity, and impulsivity must all be present for a diagnosis to be made. When comparing the systems only the ‘ADHD, combined type’ would be considered a hyperkinetic disorder. It is likely that girls, older adolescents, and adults would be less likely to be diagnosed as hyperkinetic disorder than ADHD.

The current criteria are listed in Table 30.1.

Limits of the Diagnosis of ADHD

The boundaries of ADHD are difficult to define. ADHD shares symptoms with many disorders and with typical development. At its core, ADHD is a dimensional disorder. The overlap with typical development and the lack of biomarkers has caused people to doubt the existence of ADHD as a biological entity and attribute the rising prevalence of the disorder to working parents, technology, television and environmental factors.

Other issues that limit the diagnosis relate to technical aspects. Disorders that are behaviourally defined have three issues that limit the reliability of the diagnosis. First, the same behaviour may have different names. For example, one observer may call a behaviour ‘impulsivity’, but a second observer may call the same behaviour ‘spontaneity’. In the case of ADHD this is commonly seen in the child who is described by his parents as ‘all boy’. Second, different behaviours may have the same name. Hyperactivity often is confounded by reckless behaviour. Some children with executive function difficulties have problems with planning their day while others have difficulty starting tasks. Third, different mechanisms may result in the same behaviour. Some children may not conform to classroom rules because of lack of experience while others may have significant hyperactivity.
Table 30.1 DSM-5 criteria for ADHD

People with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development:

1. **Inattention:** Six or more symptoms of inattention for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inconsistent with developmental level:
   - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities \( (e.g.\ overlooks or misses details, work is inaccurate) \)
   - Often has trouble holding attention on tasks or play activities \( (has difficulty remaining focused during lectures, conversations, or lengthy reading) \)
   - Often does not seem to listen when spoken to directly \( (mind seems elsewhere, even in the absence of any obvious distraction) \)
   - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace \( [not due to oppositional behaviour or failure to understand instructions] \ (e.g.\ starts tasks but quickly loses focus and is easily side-tracked) \)
   - Often has difficulty organising tasks and activities \( (e.g.\ difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganised work; has poor time management; fails to meet deadlines) \)
   - Often avoids, dislikes, or is reluctant to do tasks that require sustained mental effort \( over a long period of time (such as schoolwork or homework, preparing reports, completing forms, reviewing lengthy papers) \)
   - Often loses things necessary for tasks and activities \( (e.g.\ school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones) \)
   - Is often easily distracted by extraneous stimuli \( (for adults and older adolescents, may include unrelated thoughts) \)
   - Is often forgetful in daily activities \( (doing chores, running errands, returning calls, paying bills, keeping appointments) \)

2. **Hyperactivity and impulsivity:** Six or more symptoms of hyperactivity-impulsivity for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate inconsistent with the person's developmental level:
   - Often fidgets with or taps hands or feet, or squirms in seat
   - Often leaves seat in situations when remaining seated is expected \( (e.g.\ leaves place in the classroom, in the office or other workplace, or in situations that require remaining in place) \)
   - Often runs about or climbs in situations where it is not appropriate \( (in adolescents or adults may be limited to subjective feelings of restlessness) \)
   - Often unable to play has difficulty playing or engage in leisure activities quietly
   - Often "on the go" acting as if “driven by a motor” \( (e.g.\ unable to be or being uncomfortable being still for an extended time, may be perceived as restless by others) \)
   - Often talks excessively
   - Often blurts out an answer before a question has been completed \( (e.g.\ completes other people’s sentences, cannot wait for turn in conversation) \)
   - Often has trouble waiting his/her turn \( (e.g.\ while waiting in line) \)
   - Often interrupts or intrudes on others \( (e.g.\ butts into conversations or games, may start using other people's things without asking or receiving permission, may take over what others are doing) \)

In addition, the following conditions must be met:

- Several inattentive or hyperactive-impulsive symptoms were present before age 12 years
- Several symptoms are present in two or more setting \( (e.g.\ at home, school or work; with friends or relatives; in other activities) \)
- There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning
- The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder \( (e.g. mood disorder, anxiety disorder, dissociative disorder or a personality disorder) \)

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Chapter 30  Attention-Deficit–Hyperactivity Disorder and Co-existing Impairments

ADHD ACROSS THE LIFESPAN

ADHD is a life-long disorder. The manifestations of the disorder change with maturation. Parents may time the onset of hyperactivity to fetal life with increased fetal movements. Infants may show inability to regulate their states with resultant difficulty in establishing sleep–wake cycles. Impairment in self-organising may be seen in colic that is much more severe in degree or extends well beyond the typical age. Toddlers may be noted to run as soon as they walk.

Preschool is a time marked by high activity, fine motor control and play. Children with ADHD may show difficulty in circle time or playing games. Children may not learn from their experiences and be seen as oppositional. Temper tantrums may be more severe and more frequent. Some children show inability to effectively modulate sensory responses and overreact to tags, rumpled socks, loud noises or certain foods.

School-aged children must follow rules, listen to directions, complete tasks, and keep track of their belongings. Early school-aged children have difficulty with attention and academic achievement. Problems following classroom routines and fidgetiness may be noted. Early reading and mathematics difficulties are common. Maintaining friendships may be a challenge because of bossiness, inconsistent responses or behavioural modulation difficulties (humour as well as anger). Team sports may not be successful and accidents are not uncommon because of poor motor coordination, inattention and minor trauma is common and multiple shin bruises due to play are the norm. Some children may drift and get lost while the parent is shopping.

Older children express their ADHD with impulsive acts and difficulty with higher types of learning. They face organisational challenges on an ongoing basis; completing and turning in homework, chapter reading, long-term assignments are some of the expressions of disorganisation. They push beyond the limits. Deficits in the social use of language and longer than typical time for responses may be seen.

Older adolescents may not have hyperactivity but experience low boredom tolerance and subjective restlessness. Executive dysfunction predominates in adulthood with organisation, time management and planning issues. Inattention and impulsivity adversely affect driving ability.

PREVALENCE

The prevalence of ADHD continues to increase. In the USA, the National Survey of Children’s Health reported that, of US children aged 4–17, 7.8% and 9.5% were reported by their parents to have ever been diagnosed with ADHD by a healthcare provider in 2003 and 2007, respectively. The third National Survey of Children’s Health (2011–12) found that 11% of US children (6.4 million) were said to have been diagnosed with ADHD by a healthcare provider. This represents a 42% increase between 2003 and 2011 (Visser et al. 2014).

International data suggest a worldwide prevalence of 5.3–5.9% and a European prevalence of 4.6% (Le et al. 2014). A careful population-based study conducted in Rochester, Minnesota noted that the highest estimate (definite and probable) of cumulative incidence of ADHD at age 19 years was 16.0%, while the lowest estimate was 7.4% (Barbaresi et al. 2002).

ADHD is the most common neuropsychiatric condition seen by child psychiatrists, child neurologists and paediatricians. Despite the prevalence of ADHD, many children with ADHD are under diagnosed and do not receive treatment. The overall prevalence of ADHD makes it a public health focus but the increasing prevalence, increased health costs and adverse outcomes in academic, occupational and social spheres should make it a major community focus.

Why the prevalence of ADHD is increasing is unclear. The differences between European and US reports have been attributed to the differences in diagnostic criteria between the ICD and the DSM. When DSM-IV was implemented, the prevalence numbers increased because of greater recognition of inattentive ADHD, identification of ADHD in adults and adolescents, and discovery that presentations of ADHD in girls may have been more subtle. Case finding and differing diagnostic criteria do not explain the entire difference of the past 4 years. A large number of studies have sought, unsuccessfully, to identify environmental factors that are related to ADHD.

The incremental costs of caring for people with ADHD are high. The overall US annual incremental costs (in 2010 dollars) of ADHD for children/adolescents ranged from $32–72 billion, with the majority of costs attributed to health care ($21–44 billion) and education ($15–25 billion) (Doshi et al. 2012). In the Netherlands the average total cost ranged from €9860–14 483 per patient (in 2012 euros) and annual national costs were between €1.04–1.53 billion (Le et al. 2014). The majority of costs were attributed to education, followed by health care and social services. Loss of family productivity was also substantial.

As a group, people with ADHD have lower academic achievement and higher rates of retention (i.e. repeating a school year) and school non-completion (Polderman et al.
Inattentiveness was strongly related to academic outcomes. Many children, however, have sufficient academic performance and this serves to delay identification and diagnosis.

Occupational health is also adversely affected by ADHD (Küpper et al. 2012). Low frustration tolerance, irritability and impulsivity and executive dysfunction have been related to reduced productivity and workplace impairment. Adults with ADHD are at increased risk of accidents, trauma, workplace injuries and traffic accidents.

Adults with ADHD are at risk for social dysfunction. In the UK, studies of offenders indicated around 45% of young people and 24% of male adult offenders have a childhood history of ADHD and are more likely to be disruptive when incarcerated (Young and Thome 2011). In the US, ADHD is associated with more cigarette smoking and substance use disorder (SUD) (Wilens and Morrison 2011). The cigarette smoking is less likely to remit and the SUD is more likely to be more severe and chronic in duration. ADHD treatment does not appear to predispose to SUD.

Differential Diagnosis, Comorbidity and Co-existing Disorders

ADHD is defined by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity. As a diagnosis it is too narrow for clinical use. While it describes one aspect of a child’s difficulties, it is incomplete. Children with ADHD usually have additional impairments. Many of these impairments are closely tied to ADHD; either in prevalence or in manifestations. These impairments may span academic, social, emotional, behavioural, language, cognitive and motor domains. Often they require therapeutic interventions that extend beyond the attention and hyperactivity impulsivity domains.

Every professional who sees a child with ADHD will identify an area of concern related to their discipline. Parents may be overwhelmed by the long list of descriptive diagnoses that may be assigned to their child with ADHD. Other terms suggested to broaden the description of children who fall into the ADHD classification include: DAMP (deficits in attention, motor control and perception; Gillberg 2003), ESSENCE (early symptomatic syndromes eliciting neurodevelopmental clinical examinations; Gillberg 2010), encephalopathy, developmental brain dysfunction (Moreno-De-Luca et al. 2013) and a resurrection of MBD.

Some have suggested that these impairments are not independent disorders but are manifestations of the same processes that give rise to ADHD. Consequently, these impairments may not be comorbid but co-occurring (Kaplan et al. 2006). Clinicians must decide whether the child’s dysfunction represents ADHD, a disorder that mimics ADHD (differential diagnosis), ADHD and an impairment that is a co-existing disorder, or ADHD and an independent impairment (comorbid disorder). Thus a listing of the differential diagnosis of ADHD (Table 30.2) will also contain comorbid/co-occurring disorders.

<table>
<thead>
<tr>
<th>Table 30.2  Differential diagnosis of ADHD</th>
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<tbody>
<tr>
<td>Specific learning disability</td>
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<tr>
<td>Mixed receptive expressive language disorder</td>
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<tr>
<td>Tourette syndrome</td>
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<tr>
<td>Autism spectrum disorder</td>
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<tr>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Anxiety disorder</td>
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<td>Affective disorder</td>
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<td>Adjustment disorder</td>
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<td>Substance use disorder</td>
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<td>Sleep disorders</td>
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<tr>
<td>Oppositional defiant disorder</td>
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<tr>
<td>Developmental coordination disorder</td>
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<tr>
<td>Staring spells/epilepsy</td>
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<tr>
<td>Sensory integration disorder</td>
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<tr>
<td>Hearing loss</td>
</tr>
<tr>
<td>Neurodegenerative disorders</td>
</tr>
<tr>
<td>Chronic disease</td>
</tr>
</tbody>
</table>

In developing a differential diagnosis, practitioners must consider the mechanism of the observed behaviour in addition to documenting the behaviour. For example, children with intellectual disability, specific learning disabilities, autism spectrum disorders, or mixed receptive language disorders may seem inattentive or excessively active because they cannot perform at the expected level. Children with anxiety, adjustment or affective disorders may be otherwise occupied and seem inattentive. Physiological derangement as in hearing loss, or thyroid, sleep or neurodegenerative disorders may mimic ADHD.

The interaction of multiple factors may need to be considered. Most often clinicians have to weigh the relative contributions of attention, anxiety and language in the diagnostic process. Sometimes this does not clarify until a course of therapy is undertaken.

Specific Learning Disabilities

Specific learning disabilities (SLD) are characterised by difficulty in acquiring and using academic skills at an age-appropriate level. The difficulty is not due to intellectual limitations or lack of instruction. SLD are complex constructs that may affect reading, mathematics and written expression. They may occur singly or in combination. ADHD is often seen in combination with SLD. Learning disorders and ADHD were noted in 3.7% of a national sample (Pastor and Reuben 2008). Children with isolated SLD may exhibit behaviours consistent with ADHD.

Specific reading disability may assume a number of different forms in children with ADHD. Younger children have...
difficulty with basic reading (decoding). Often their deficit is in blending the sounds into words. Older children may have difficulty extracting meaning from text. While they can read every word on the page they do not derive meaning from what they have read. Clinically, students may report, 'I spent two hours reviewing that chapter and still failed the test'. Specific reading disability is linked closely to language abilities (McArthur et al. 2000, Snowling and Hulme 2012) and is also common in ADHD (Sexton et al. 2012). Clinical samples suggest that the prevalence of ADHD in children with specific reading disability approximates 40% (Hart et al. 2010). Rates of ADHD in children with specific reading disability range from 9% to 60%. Population studies suggest rates of 9–42.5% (Yoshimasu et al. 2011). SLD affecting written language is also common in ADHD. Approximately 60% of children with ADHD have disorders of written expression (Yoshimasu et al. 2011). These disorders may be due to difficulty with fine motor, language or organisational dysfunction that is seen often in ADHD. Children with ADHD also are at higher risk for mathematics difficulty (odds ratio = 2.55) (Czamara et al. 2013). Children with ADHD symptoms may misread addition and subtraction signs, misalign columns and not recall multiplication tables. They have difficulties with mental mathematics due to working memory deficits and timed quizzes.

Language Disorders
Language disorders show (see Chapter 31) persistent difficulty in the acquisition or use of language. Symptoms of ADHD show considerable overlap with disorders of communication. This overlap is further complicated by the independent relationship between SLD and language. It is extremely difficult to extricate the contributions of attention, language, working memory and anxiety to a child's performance on an assessment instrument.

The relationship between language disorders and ADHD is bidirectional (Sundheim and Voeller 2004). Half of children with ADHD have language disorders and half of children with language disorders have ADHD. Difficulty in processing language shows similar symptoms to inattention. Excessive talking and interrupting others is seen in both ADHD and Social Communication (pragmatic) language disorders.

Autism Spectrum Disorder
Autism spectrum disorder (ASD) and ADHD overlap the social border. ASD is characterised by deficits in social communication and interaction, and restricted, repetitive behaviour, interests or activities (APA 2013) (see Chapter 29). Children with ADHD may evidence some of the characteristics that define ASD. For example, it is not uncommon for children with ADHD to exhibit variable responses to social interactions because of inattention or impulsivity, poor eye contact, misreading social cues and difficulty maintaining friendships. Difficulties modulating responses to sensory stimuli are not specific to ASD and may be seen in ADHD.

In the past, the presence of autism spectrum disorder excluded the diagnosis of ADHD. More current research shows a bidirectional relationship between ADHD and autism spectrum disorder. Studies suggest that from 20% to 30% to up to 78% of children with autism meet criteria for ADHD (Murray 2010; Taurines et al. 2012). A study of children with ADHD showed that 20% exhibited autistic traits (Kotte et al. 2013). The overlap of ASD with ADHD is in part due to cognitive, language and anxiety issues but children who ‘outgrow’ the ASD diagnosis evidence executive dysfunction and increased levels of impulsivity (Troyb et al. 2014) and some meet criteria for ADHD.

Tourette Syndrome
Tourette syndrome is a triad of multifocal tics, ADHD and obsessive compulsive features (see Chapter 20). The presenting symptom may be the tics, the ADHD or the obsessive compulsive features. The other features may develop or diminish as the child matures. While tics may develop in association with stimulant medication, children with ADHD should be monitored for the appearance of tics and obsessive compulsive features.

Intellectual Disability
Children with intellectual disability may exhibit behaviours that can be interpreted as being consistent with ADHD. While most intellectual disability is identified in the preschool period, some children with milder or borderline degrees of cognitive limitation are not diagnosed until primary school. These children may have difficulty following complex instructions and classroom routines, organising tasks, exhibit reluctance to engage in tasks that require sustained mental effort, and seem distractible or forgetful because they do not fully understand the tasks.

Intellectual disability does not exclude ADHD. Many children with intellectual disability meet criteria for ADHD. Using ICD-10 criteria, the prevalence of hyperkinesis in children with intellectual disability was 8.7%, almost ten-fold more than for children without intellectual disability (Emerson 2003).

The DSM qualifies the inattentive and hyperactive domains by requiring function that is not appropriate to developmental level. It does not provide guidance as to how to determine this. Consequently, determining whether children with mild intellectual disability also meet criteria for ADHD may be difficult. For those children it may be prudent to deemphasise the diagnostic process and undertake a therapeutic trial under close monitoring (Simonoff et al. 2013).

Anxiety, Affective and Adjustment Disorders
ADHD commonly coexists with childhood psychiatric disorders. Anxiety, affective and adjustment disorders share symptoms with ADHD. They all may manifest academic underachievement but have different underlying mechanisms.
The inattention that is seen in anxiety disorders is attributed to worry and rumination while that of ADHD is due to attraction to external stimuli or preoccupation with enjoyable activities (APA 2013). Children with depressive disorders have difficulty concentrating when they are experiencing a depressive episode. Increased activity may be seen with bipolar disorder. ADHD is a frequent co-existing condition of disruptive mood regulation disorder but pervasive irritability is not a predominant feature of ADHD.

Anxiety, affective and adjustment disorders also coexist with ADHD. Approximately 25% of children with ADHD have anxiety disorders (Schatz and Rostain 2006), while depressive disorder may be present in 20% (Green et al. 1999). Adjustment disorders may be seen in children who are defeated, experience substantial negative expressed emotion, or chaotic social situations.

Oppositional Defiant Disorder

Oppositional defiant disorder (ODD) is often diagnosed in conjunction with ADHD. Approximately one-third of children with ADHD have co-existing ODD (Green et al. 1999). Young children who are in situations where they are chronically unable to perform or who are usually unable to complete tasks may exhibit the angry mood/irritable features and argumentative behaviour that defines ODD, but are more correctly considered adjustment disorders. Non-conformance with requests must be interpreted in relation to the child’s abilities and recognise the variable performance of children with ADHD. Children with the diagnosis of ODD should be evaluated for ADHD.

Substance Use Disorder

Substance use disorder may be associated with disorganisation, poor time management and inattention. Impulsivity and hyperactivity may be present with certain substances. While people with ADHD are at risk for substance use disorders, the sudden onset or worsening of pre-existing symptoms should lead the clinician to the correct diagnosis.

Sleep Disorders

The association between sleep disorders (see Chapter 18) and ADHD is unclear (Yoon et al. 2012). ADHD symptoms, particularly inattention, are seen in primary sleep disorders – excessive daytime sleepiness, restless legs syndrome, periodic limb movement in sleep, sleep disordered breathing and obstructive sleep apnoea. Twenty-five to fifty per cent of children with ADHD have sleep problems. Sleep deprivation can mimic or exacerbate ADHD symptoms but it is not clear that it causes ADHD.

Staring Spells/Epilepsy

Inattention is often manifested by staring spells. Staring spells may be seen in ADHD but are also noted in daydreaming, migraine (see Chapter 17), or absence seizures (see Chapter 16).

Most staring episodes are not epileptic; however, epilepsy must be excluded as a cause of inattention. Absence seizures are associated with short (<20 seconds) staring spells, no aura or postictal drowsiness. Electroencephalographic studies with hyperventilation will help distinguish typical absence from atypical absence seizures. Staring spells that last longer than a minute and are associated with aura and postictal drowsiness may be focal seizures with impaired awareness. Absence seizures may be further separated into typical absence or atypical and absences with special features. While epilepsy is not common in children with ADHD, ADHD is seen in approximately one-quarter to one-third of children with epilepsy (Cohen et al. 2013; Masur et al. 2013).

Developmental Coordination Disorder

Disordered motor coordination and ADHD overlap about 50% of the time (Martin et al. 2006). Motor coordination issues were part of minimal brain dysfunction and included in DAMP (deficits in attention, motor control and perception) (Gillberg 2003). Falling, bumping into things and knocking things over may be due to deficiencies in motor control, impulsivity or hyperactivity. Postural instability may be misperceived as fidgetiness. Developmental coordination disorder may underlie the written language disorders and the dysarthria seen in children with ADHD.

Sensory Processing (Integration) Disorder

Sensory integration disorder is characterised by inappropriate or deficient sensory processing. Clinically, it manifests as under or over responsiveness to sensory stimuli. Children may be overwhelmed by loud noises, irritated by tags or rumpled socks, or display aversion to certain foods or smells. They may seek out certain clothing textures, crave roughhousing/wrestling, need to touch everything and be excessively affectionate. Motor dysfunction that is similar to DCD forms a subtype of sensory processing disorder. Whether sensory processing disorder is an independent disorder is still being debated. In addition to ADHD, sensory integration issues are seen in autism spectrum disorder, developmental coordination disorder and anxiety disorder (AAP et al. 2012).

Hearing Loss

Conductive hearing losses (see Chapter 23), such as those associated with otitis media are not usually associated with disorders of attention or learning. Sensorineural hearing loss, on the other hand, may be progressive in nature and may impair communication. The child with a hearing loss may have difficulty sustaining attention in tasks, does not listen when spoken to, does not follow through on instructions, may seem distracted, and may exhibit behaviour that is deemed forgetful or not giving attention to details. Special care should be taken to ensure adequate hearing in children who present with primarily inattentive symptoms.
Neurodegenerative Disorders

Symptoms of inattention, poor organisation and hyperactivity/impulsivity may be present early in the course of neurodegenerative disorders. Some children with adrenoleukodystrophy have been diagnosed as having ADHD before the full scope of the disorder became apparent. A history of worsening symptoms should raise a consideration of a progressive neurological process.

Elimination Disorders

Encopresis and enuresis are more common in ADHD than in the general population. Enuresis may be confined to nighttime wetting. In younger children, however, it is not uncommon to see the child rushing to the bathroom because the child was not reading his or her bodily signals properly and was preoccupied. Daytime urinary incontinence is associated with ADHD, while night-time enuresis does not put a child at increased risk of ADHD (von Gontard et al. 2011). Daytime enuresis is most often treated behaviourally while night-time enuresis may require pharmacological intervention.

Children with ADHD have increased rates of constipation and faecal incontinence when compared to children without ADHD. Faecal incontinence was uncommon in children with ADHD (0.9%) but was approximately six times more common than in children without ADHD. Children with ADHD had more visits than those without ADHD for both constipation and faecal incontinence.

EVALUATION

The diagnosis of ADHD rests on its behavioural characteristics. The diagnostic process is much more than an enumeration of symptoms. The clinician must elicit the symptoms from at least two sources and then interpret them. The age at onset, duration and the functional limitations caused by the symptoms must be established. Other conditions that have similar symptoms must be considered and incorporated into the diagnostic formulation. Exclusionary disorders must be appropriately diagnosed.

Behavioural checklists may assist the diagnostic process but they do not replace it. The limitations of behavioural checklists have been enumerated (Shapiro 2001). Checklists that are wide-ranging do not focus on ADHD. Those that focus on ADHD may miss important co-existing conditions.

ADHD checklists do not provide context. Parents do not have a point of reference upon which to base their responses. A very active child may have a negative checklist because his brother is much worse. The checklists do not quantify behaviour. How many fidgets equal a ‘very much’?

Reporter bias is a problem for behavioural checklists. While most checklists are supposed to represent a sample of behaviour for an extended period before the list is completed, most reporters focus on the day or two before the visit. Yesterday’s behavioural flare may obscure 3 months of good progress. The variability exhibited by children with ADHD make it difficult to capture behaviour with a single descriptor. Another bias arises because most of the symptoms are listed as negatives. Parents have difficulty reporting that many negative attributes of their child and blunt the extreme responses.

Inter-rater reliability of behaviour checklists is poor. Parents and teachers often do not agree on the child’s behaviour. The results on checklists may vary widely when a child has multiple teachers and individually completed checklists are obtained. This may reflect the bias of the reporter, the variability of the child, the demands of the class, or characteristics of the interaction of the child and teacher.

The lack of the homogeneity of the ADHD syndrome and the large number of related disorders mandate that symptoms must be obtained through skilful history taking and then interpreted by knowledgeable professionals to establish the proper diagnosis. Direct verbal interaction is the best way to establish the diagnosis of ADHD but it is time consuming and inefficient. Behavioural checklists may be adjunctive methods for obtaining information but they do not establish the diagnosis of ADHD.

AETIOLOGY

ADHD is a final common pathway of multiple pathologies. Most cases have a hereditary component but ADHD is also seen in association with many different brain insults and disorders. Prenatal exposures to alcohol, tobacco and illicit drugs have been associated with ADHD. Preterm birth, iron deficiency, lead exposure, mercury toxicity and thyroid disorders are associated with ADHD and academic dysfunction. Epilepsy, cerebral palsy, spina bifida, migraine, traumatic brain injury and brain infections are strongly related to difficulties with attention and executive function.

Searching for the aetiology of a person’s ADHD has a low likelihood of establishing a cause and a lower likelihood of altering the treatment approach. Investigations that seek to determine the cause of ADHD have been unsuccessful. There is no consistent biomarker that will make the diagnosis of ADHD. There is a strong hereditary component to ADHD, but whole exome sequencing studies have failed to yield consistent findings. Candidate gene analyses have revealed statistically significant results, but only account for a small percentage of the variance. Neuroimaging studies, while illuminating brain behaviour interactions, have not yielded consistent results. Electrophysiological approaches have held promise but are not clinically applicable. Metabolic studies have not been useful. Despite this, the medical and psychological evaluations of ADHD may prove useful in identifying important co-existing conditions that will affect the management plan.

Medical Evaluation

The majority of the medical evaluation follows the schema outlined in Chapter 28. It should include family history,
significant past events, complete review of systems, developmental and school history and behavioural history with a specific focus on ADHD. Early infancy manifestations of ADHD relative to state and activity should be noted. Inquiries relative to attention should not only focus on the primary symptoms of ADHD but also develop a picture of a child who has difficulties with the processes upon which ADHD is built. Questions about attention should extend beyond short attention and encompass over-focusing, perseveration, difficulties with transitions and variability of performance (‘Some days he hits on all eight cylinders and some days he hits on three’). Factors that modify the attentional problems should be noted.

Distractibility may include questions relating to unfinished activities that are started, multitasking, minding other people’s business more than his own, participating in conversations that are taking place in the next room. Asking how many times the child has been misplaced while the parents are shopping is a question that often yields a positive response and serves as an entry point to talking about distractibility. Another dimension of distractibility relates to environmental distractions such as the furnace starting, or someone closing a door or being disturbed when the child’s sibling quietly walks across the kitchen as the child is attempting homework. A third dimension is not paying attention to the task at hand and observing relationships that are not appreciated by others. For example, noticing a pattern in wood siding when people are walking down the aisle at church. This may be mistaken for creativity. Impulsivity is often manifested as blunting out in church, not using an ‘inside voice’ or running after a ball into the street between parked cars.

Questions about social interactions focus on whether friendships can be established and maintained, age of friends, types of activities that are enjoyed. Other questions may focus on organisation (‘Is your child’s room a mess?’), time sense (getting ready for school in the morning), completion of chores and boredom.

Mental health status should be queried. Mood, worries, depressive symptoms, routines and stereotypies should be included. Can the child modulate humour or anger? Qualitative assessment of the frequency and severity of anger/tantrums and the post tantrum insight are important aspects to consider. Stealing, fire-setting and cruelty to animals are not usually part of ADHD.

The child’s activity level should be noted. While absence of hyperactivity in an office setting does not exclude it in the classroom, its presence supports the diagnosis of ADHD. Fidgetiness and restlessness is more frequently seen but may be due to anxiety related to the evaluation. Tics may take the form of exaggerated eye blinks, throat clearing or shoulder shrugs. Lapses of attention and staring spells may be an indication for hyperventilation manoeuvres if there is no history of cerebrovascular disease, hypertension, sickle cell disease or trait, or severe asthma.

Assessment of the child’s use of language yields important information. Can the child follow the instructions for the examination or is visual demonstration required? Is the vocabulary age appropriate? Are modifiers (adjectives and adverbs) used? Can the child tell an organised story with a beginning, middle and end? Can the child tell or understand a joke?

The physical examination should include growth parameters (including head circumference), a comprehensive physical examination including a focus on dysmorphisms, and a complete age-appropriate neurological examination. Physical findings often show subtle asymmetry of growth of the face, chest (downward and lateral displacement of the nipple) and leg. Tone is usually decreased and asymmetrical. Occasionally leg tone is increased compared to arm tone.

Soft neurological signs are developmental signs that are not diagnostic or localising but occur more frequently in ADHD. There are many of these signs but in composite they serve to demonstrate subtle abnormalities of tone, symmetry, or coordination. They have prognostic ability and relate to later behavioural outcomes. Previously, they were thought to distinguish functional from organic disorders.

Neuropsychological evaluation is not required to establish the diagnosis of ADHD. A comprehensive neuropsychological evaluation is useful for delineating the dysfunctions in learning and behaviour that are associated with ADHD and identifying disorders that mimic ADHD. Speech and language evaluations are useful in discerning difficulties in language usage, pragmatics and connected language. Educational specialists may augment the neuropsychological evaluation by using instruments that emulate the classroom experience and making recommendations that are directly applicable to classroom function. Occupational therapists can quantify fine motor dysfunction and make recommendations about compensatory and circumvention strategies that may be employed to bypass the DCD. They may also address sensory processing disorders.

**MANAGEMENT**

The management of the child with ADHD requires creativity, persistence and a long-term perspective. There are a large number of dysfunctions that accompany the diagnosis of ADHD. Fortunately, not every child has every dysfunction. In addition, all children who have accompanying dysfunctions do not have them to the same degree. This means that there is no ‘garden variety’ of ADHD and that programmes must be individualised. ‘One size fits all’ approaches will fail.

The foundations of a successful management programme are: delineation and treatment of associated dysfunctions, knowledgeable parents, educational accommodations, maintenance of the child’s self-esteem and medication.

**Delineation and Treatment of Associated Dysfunctions**

ADHD is functionally defined and, thus, is a final common pathway. It has multiple aetiologies and many associated dysfunctions that are present to varying degrees. These disorders
may limit function in the absence of ADHD. Indeed, they may be the initial diagnostic focus and the ADHD identified as a comorbid condition. There is limited data that suggest that ADHD in combination with associated dysfunctions have worse outcomes than ADHD or the associated dysfunction occurring separately (Sexton et al. 2012). The reasons for this observation have not been elucidated. However, associated dysfunctions may be impairing by themselves and therefore, impact the ADHD management programme.

If the associated dysfunction is severe, the goals of the management programme may have to be adjusted. For example, if the ADHD is associated with severe intellectual disability, independent function as an adult is unlikely. The coexistence of a specific reading disorder may limit literacy and, ultimately, vocational choices.

Failure to recognise associated dysfunctions may delay treatment and result in suboptimal outcomes. Some associated dysfunctions may be masked by the ADHD. Anxiety may be mistaken for inattentiveness or hyperactivity. Other associated dysfunctions may not be evident until situational demands increase. Disorders of written language may not be evident in early elementary school when the tasks require only limited pencil control but they may be devastating to older students who are required to take notes in class. Associated dysfunctions, such as tics, may require ongoing monitoring but only intermittent interventions.

**Knowledgeable Parents**

Knowledgeable parents are key to a successful management programme. They will know ADHD, know how to deal with their child’s ADHD, effectively advocate for their child, and identify and establish relationships with the practitioners who work well with their families.

Parents must recognise that ADHD is a neurodevelopmental disorder and not the result of poor parenting, dietary imbalances, immunisations, or lack of sleep. They should know how to make the diagnosis of ADHD, the symptoms that define the syndrome and the broader aspects of ADHD. Parents should realise that ADHD has many expressions and that each child is unique. Children with ADHD are not lazy, stupid or oppositional, and parents should consider that their child’s failure to complete a task may be because the child is unable and not unwilling. They should be aware of the variability that is seen in ADHD; the child is not out to ‘get them’.

Parents should not only know text book ADHD, but also know how their child expresses the disorder. Some children get overwhelmed and cannot plan multipart tasks such as cleaning their room. ‘Place your dirty clothes in the hamper’, ‘Put your books on the shelf’ and ‘Put your toys away’ are more likely to have positive results than ‘Clean your room’. Setting out clothes for school the night before, using a checklist for morning activities and ensuring that completed homework is in the book bag are effective techniques that parents have used.

Children establish different routines. Some have to attend to homework as soon as they come home and complete it before dinner. Others need time to place their brain in neutral in front of a screen (television or videogame) and recover from the tremendous effort required to perform in school. Children may find the question ‘How was your day in school?’ to be intrusive and overwhelming. Parents who encounter this may do well to delay the question until the information comes out spontaneously or ask it at a time when the child is relaxed.

A knowledgeable parent can advocate for their child. They need to negotiate accommodations with the school, extracurricular activities and social situations. They need to identify and choose practitioners who are used to managing children with ADHD. Parent groups, particularly those with professional advisory boards, are useful sources of information. The sharing of information and experiences by parents provides a filtered source of information that often provides useful answers than random internet searches.

**School Accommodations**

Most children with ADHD can have their educational needs met in a general education setting with accommodations. In contrast to children with specific learning disabilities, children with ADHD are able to master the content but experience academic underachievement because inattention, hyperactivity and impulsivity impede the educational processes. Some of the accommodations used are for behaviour, some for organisation and some for disorders of written expression. Special education services should be reserved for students with SLD, autism spectrum disorder or intellectual disabilities.

Students with ADHD do better with active learning. Classroom discussions, study partners, simulations, movies and CDs, field trips and experiments are preferred over textbook or lecture-based learning. Some children require environmental modifications; seating away from the windows, doors, or noisy students, or near the teacher. Extra time, frequent breaks and alternative methods of evaluation serve to ensure that the student can demonstrate their capabilities.

Homework is a common cause of strife. The student should develop a routine for doing homework with guidance from the parents. If the written language demands are an impediment, they should be circumvented by a parent acting as a scribe. If the work load is too great, then negotiations with the teacher should take place to determine the minimum amount that is required to meet the educational objectives and demonstrate mastery of the material. A folder with two pockets, one for incoming work and the other for outgoing, will help ensure that completed homework will get to the proper place.

**Maintenance of Self-Esteem**

Children with ADHD face many challenges. Often they do not measure up in family, academic or social domains. In
families that are not knowledgeable about ADHD, they may be perceived as the ‘behaviour problem’. Their impulsivity, hyperactivity, inattention, poor pragmatics, dysmodulation and variability may create social issues with age peers. The academic difficulty that students with ADHD experience is well known.

Children with ADHD should be closely monitored for symptoms of defeat. Self-deprecating remarks such as ‘I am dumb’, ‘I have no friends’, ‘Nobody likes me’ or ‘Why can’t I be like …’ are cause for concern. More worrisome are the statements ‘This family would be better without me’ or ‘I wish I were dead’.

A preventive mental health approach is often successful. Defining roles wherein the child can successfully participate is a vital part. Chores are useful family interventions. If the child cannot set the table because he or she is too clumsy with the glassware, he can set the knives and forks. If the child cannot set the table because he or she is too young or too tired, the family can decide to use paper cups. Allowances should be provided and should be contingent on chore completion. They are tangible demonstration of worth but may have to be paid more frequently than weekly and conditions established to enable partial payment. ‘First born privileges’ are those privileges that are accorded to the older child because of his age. They serve to limit conflict when younger children are performing as well or better than their older sibling. In the school setting the child with ADHD can be the messenger that makes deliveries to the office. Older children may assist with announcements or act as a crossing monitor. Extracurricular activities need to be chosen carefully. While some children with ADHD excel at sports many do not. Team sports are particularly difficult because of the additional social aspects. Sports where the individual’s progress is measured against themselves, such as martial arts, cycling, running or swimming, may be preferred. Some children bypass sports and choose music, drama, photography or art. Others develop interests that are further off the beaten path, such as nature, chess, woodworking, hunting or fishing, or choose to interact with older or younger children. Scouting and church youth groups offer adult supervised activities, but the leader needs to have experience working with children who have ADHD.

Medication

Stimulants are the pharmacological foundation of ADHD treatment. No behavioural or alternative medicine intervention is more effective in treating ADHD. Stimulants are relatively free of side effects and have no demonstrated long-term adverse effects. Stimulants used for ADHD either belong to the methylphenidate or amphetamine class of drugs. Methylphenidate may be found in short-acting, long acting, single isomer, liquid, capsule and transdermal forms. Amphetamine may be found in short-acting, long acting, liquid, capsule and a pro-drug form. Second-line drugs for ADHD are alpha adrenergic agents (guanfacine and clonidine), atomoxetine and bupropion. The use of tricyclic antidepressants and pemoline have been markedly curtailed because of associated fatalities.

Just as other aspects of ADHD management must be individualised, it is also true of medication management. The effective dose must be determined empirically. It is not weight dependent. There is variability in the duration of drug effect. Some young children have a prolonged drug effect and may only require single day dosing of short-acting agents. Other children may metabolise the agent more quickly and need multiple doses. The timing of the dose may also vary according to the student’s needs. College students who have a first class at 11am may not need to take stimulants at 7:30am while an elementary school student who starts class at 8:15am will.

When the stimulant effect wears off some children exhibit rebound. They may return to their unmedicated state with return of the inattentive and hyperactive/impulsive symptoms. Occasionally the rebound is more severe than the baseline condition. Some children are discomforted by rebound because they do not feel in control of themselves. Homework and extracurricular activities may be more difficult. Children who are rebounding may experience difficulty settling for sleep because they cannot stay still or organise for sleeping. This has lead people to incorrectly conclude that the stimulants are responsible for the insomnia. In fact, a short-acting dose of stimulant in the late afternoon will facilitate homework, extracurricular activities and sleep.

Families may choose not to administer stimulants on the weekend and when school is not in session. This may be ill advised for children who squirm too much in church, have to do homework, or who have social interaction difficulties that are due to their ADHD. In addition, the moodiness that is occasionally encountered when a child initiates stimulant therapy may be prolonged by intermittent administration.

The most common side effects of stimulants are moodiness when the medication is initiated, anorexia, insomnia and tics. Most children have appetite suppression while on stimulants. Medication duration can be judged by monitoring when the child begins to eat. Tics are associated with stimulants. There is no evidence that stimulants cause the tics or that once a child has tics that stimulants worsen them. Some of the children with tics have Tourette syndrome but presented with ADHD symptoms. Changing stimulants or using a second-line drug may ameliorate the tics. Insomnia and other sleep disturbances are common in children with ADHD and may not be related to stimulants. Rebound must be considered when evaluating difficulty settling for sleep in children with ADHD. Less common side effects include over-focusing, sadness, headaches and stomach aches. The less common side effects may be ameliorated by lowering the dose or ensuring a late afternoon snack. Stimulant use in childhood has not been found to be linked to later substance use disorder.

The key questions about stimulants are when to start and when to stop. Starting the medication is a joint decision between parents and physicians. Usually stimulants are used for a defined time and the effects and side effects are monitored.
At the end of the trial it is determined that the effect is sufficient to merit continuation or not. Stimulants may have dramatic effects on student performance but normalisation of function is uncommon. Consequently the other aspects of the management programme must be in effect for successful outcomes.

Adolescents often decide to discontinue their stimulants. Part of this decision is the result of normal adolescent behaviour – ‘There is nothing wrong with me’. Part is due to the perception that stimulants blunt the adolescent’s ability to socialise; decreased impulsivity is perceived as a lack of spontaneity. If an adolescent is desirous of stopping stimulants, then it is necessary to jointly develop criteria for continuing without medication or for reinstitution of stimulant therapy.

Further information on the pharmacological management of ADHD can be found at www.nice.org.uk/guidance/cg72/evidence.

ADHD is a neurodevelopmental disorder that is defined by developmentally inappropriate levels of hyperactivity/impulsivity and inattention. It usually is accompanied by cognitive, language, behavioural and emotional disorders and is expressed in family, academic, social and occupational domains. ADHD is best addressed with a multimodal approach that involves parental education, school accommodations, maintenance of self-esteem and medication. ADHD is a life-long disorder.

Management programmes must be modified to address the changing demands associated with maturation. The challenges associated with transitions are known and can be addressed proactively. Programmes must be modified to address the increased demands of school, more subtle social interactions and the emerging desires of the patient that occur as the child ages.

REFERENCES


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Disorders of speech, language and communication can either emerge during language acquisition in the developmental disorders or follow the onset of acquired disease. They are a ‘mark of a wide range of physical and developmental problems’ (McLaughlin 2011): within the developmental conditions the term ‘primary’ denotes that speech and/or language disturbance is the principle or only problem while the term ‘secondary’ refers to where it is associated with a wide range of conditions which include intellectual impairment (Shevell 2003; Riou et al. 2009), autism spectrum disorder (ASD) and sensory neural hearing loss (O’Hare 2009a; Pimperton and Kennedy 2012). The distinction is helpful but not always immediately apparent from the clinical features as secondary conditions may masquerade as primary when speech is affected before the more classic symptoms emerge, exemplified by delayed speech milestones before motor deterioration in Duchenne muscular dystrophy. Secondary causes may also have distinctive features which suggest a primary cause but are nevertheless characteristic of a particular syndrome with wider implications such as in 22q11 deletion where velopharyngeal insufficiency, hypernasal phonation and verbal dyspraxia may initially suggest a primary speech production difficulty (Shprintzen 1997).

Although speech, language and communication can be separately assessed most of their disturbances have some degree of overlap. Within the acquired disorders this often follows the diffuse nature of the insult to the developing brain whereby, for example, dysarthria, dyspraxia, dysfluency, dysphonia and dysphasia may together impair speech intelligibility following traumatic brain injury. In developmental situations the distinction may be difficult to apply because of the hypothesised cause: phonological speech delay/disorder problems, when the difficulty aligning speech sounds into intelligible speech, is considered linguistic or language based in nature. Another example would be verbal dyspraxia, where despite the same underlying genetic abnormality individuals in one family have severely affected speech in a relatively isolated fashion and yet in most other family members there are associated significant deficits in language and cognition (Lai et al. 2001). Finally, the distinction between developmental and acquired can be difficult to apply in some conditions that appear to have a very early onset or are associated with anomalies on cranial imaging as seen in some of the pseudo bulbar palsies. Despite this the broad division into developmental and acquired has some merits, bringing structure to the discussion of disorders of speech, language and communication, as well as being informed by international classifications.

**DEFINITION**

Language is a system for communication acquired through usage (Tomasello 2003). Speech is simply one mechanism for expressing a language, and components are defined in Figure 31.1. A language relies on symbols sequenced with a desire to employ these to share attention with another, the latter being an important pre-linguistic skill termed ‘joint attention’ (see Chapter 29). Gesture, sign and/or iconic symbols can be alternative methods to speech with which to communicate.

The most common conditions that specifically disrupt acquisition of language are primary developmental disorders of speech and language defined on inclusionary and exclusionary criteria. A number of definitions exist but all specify some level of significance to the measure of how delayed the child is in comparison to their peers. The exclusionary criteria operate discrepancy concepts such as language delay in the presence of a normal nonverbal IQ and an absence of an alternative explanation for the impairment.

Although current classifications tend to composite speech and language features to determine inclusionary criteria an alternative is the classic neurological criteria based on the features of the affected speech and language, for example, syntactical/lexical or semantic (Rapin 1996). Speech therapists/pathologists will also define conditions on the basis of speech and language...
inclusionary criteria which may include comments about the speech sound system with reference to whether the child is employing a speech sound range that would be recognisable in a younger child, the so called ‘delay’ or whether it is ‘disordered’ and would not be observed in the normal development of speech sound inventory. Children therefore may have widespread inclusionary difficulties affecting the processing of phonological, semantic or syntactic information in the exclusionary presence of normal intelligence and an adequate learning environment, as well as in the absence of a neurological disorder, hearing problem or primary emotional difficulty.

Table 31.1 illustrates the normal progression of mastery of speech sounds in the phonetic English language.

The two main clinical classifications that define speech, language and communication disorders are the ICD-10 (WHO 1992) (Table 31.2) and the DSM-5 (American Psychiatric Association 2013). The ICD-10 approach of distinguishing between receptive, expressive and mixed disorder has been redefined within the DSM-5 where language disorder is now subsumed under communication disorders and includes language disorder, speech sound disorder, childhood-onset fluency disorder (stuttering), social (pragmatic) communication disorder and unspecified communication disorder. The definition of language disorder still covers inclusionary criteria but incorporates the concept of ‘persistent difficulties in the acquisition and use of language across modalities (i.e. spoken, written, sign language or other) due to deficits in comprehension or production’ and ‘language abilities that are substantially and quantifiably below age expectations’. The definition of speech sound disorder has the key diagnostic criterion of ‘persisting difficulty with speech sound production that interferes with the speech intelligibility’.

The category of dysfluency refers to a disorder manifest by repetitions of sounds, syllables and words with prolongations of sounds. There may also be difficulty initiating the voice or silent blocks with avoidance of certain words or speaking situations and the presence of associated body or facial
Chapter 31 Disorders of Speech, Language and Communication

Table 31.1 Progression of the mastery of speech sounds in phonetic English language

<table>
<thead>
<tr>
<th>Age</th>
<th>Expected speech sounds and processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>p, b, t, d, n, m; Omitting of final consonants e.g. ‘tap’ -&gt; ‘tar’</td>
</tr>
<tr>
<td>12 months</td>
<td>Consonant harmony e.g. ‘dog’ -&gt; ‘gog’</td>
</tr>
<tr>
<td>18 months</td>
<td>Reduplication process e.g. ‘bottle’ -&gt; ‘bobo’</td>
</tr>
<tr>
<td>2 years</td>
<td>The addition of w: Consonant harmony e.g. ‘duck’ -&gt; ‘guik’ should still be omitted</td>
</tr>
<tr>
<td>2½ years</td>
<td>Process of fronting e.g. ‘car’ -&gt; ‘tar’</td>
</tr>
<tr>
<td>3 years</td>
<td>Consonant blends are reduced ‘spoon’ -&gt; ‘poon’</td>
</tr>
<tr>
<td>3½ years-4 years</td>
<td>Most sounds are now heard but emerging ones do include k, g, sh, ch</td>
</tr>
<tr>
<td>5 years</td>
<td>Processes include fronting e.g. ‘cat’ -&gt; ‘tat’</td>
</tr>
<tr>
<td>5½–7 years</td>
<td>Most sounds are correct</td>
</tr>
<tr>
<td></td>
<td>Processes are still evident ‘th’ -&gt; ‘f’ e.g. ‘thank you’ becomes ‘fank you’ and ‘rabbit’ becomes ‘wabbit’</td>
</tr>
<tr>
<td></td>
<td>Some ongoing speech sound difficulties with ‘r’ and ‘th’ may be ongoing</td>
</tr>
</tbody>
</table>

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Dysfluency can be a normal process observed between the age of 3 and 5 years, however, a diagnosis of a speech fluency disorder would be appropriate when symptoms persist for more than a few months and became longer term. A family history of dysfluency is associated with this risk of developing chronicity.

The DSM-5 also distinguishes children with pragmatic language impairment as discrete from those with ASD (see Chapter 29). While these children with pragmatic impairment experience day to day problems in their use of language for communication they do not have the degree of social interactional and restricted repetitive behaviours that characterise those affected by ASD.

In addition to these common disorders of speech and language there are some rare and severe conditions in which speech production is affected with what appears to be a significant motor component. Childhood apraxia of speech or verbal dyspraxia, as it is sometimes termed, still generates debate as to what exactly is the underlying deficit, but for many affected children there is disruption of temporally and spatially drive placement of the articulators or a disruption of motor planning for speech. The clinical picture can be complicated by elements of dystarhria where there is weakness or involuntary movements affecting articulation more commonly encountered in acquired disorders. Problems with phonation and control of the voice projection and integration of breathing may amplify the unintelligibility.

Finally, with particular reference to neurological paroxysmal disorders DSM-5 now defines a group of speech and language disorders associated with new-onset epilepsy. These are examples of conditions that can appear to straddle developmental and acquired categories with the range including early delay in the under-3-year age group, expressive and receptive language disorders, speech disorders, disorders of social communication (without autism) and dysfluency. It has been proposed that some types of anticonvulsants exacerbate the speech difficulties (Pal 2011). (See Chapter 16.)

PREVALENCE

Around 15% of 2 year olds have delayed speech and are designated as ‘late talking toddlers’ (Law et al. 2003; Desmarais et al. 2008; Buschmann et al. 2009; O’Hare 2009b; Reilly et al. 2010; O’Hare and Bremner 2016) with causes multifactorial although these toddlers are more likely to have a family history of delayed language acquisition. There is also a relationship between late talking and socioeconomic and parental factors such as poverty and low maternal education with the former also having a relationship with reduced social skills and problems with behaviour although the causal direction is unclear (Desmarais et al. 2008). Although clinical studies identify what appear to be risk factors for speech and language delay such as male sex, family history and preterm birth (Boyle and Boyle 2013), as well as possible good agreement between parent report and direct assessment of children’s abilities at 2 years of age (Johnson et al. 2008), there is no evidence that targeted screening for speech and language delay would result in better identification or outcomes (Nelson et al. 2006) and so it is not presently recommended. Most children, therefore, are identified through surveillance or clinical presentation (Kasper et al. 2011).

Children in early school with a phonological difficulty with persistent deletion/substitution errors in their speech have an increased risk of difficulties in reading, spelling and other academic areas that can persist. In addition, persistent speech production problems have been reported as posing an increased risk for social acceptability in school. The prevalence of speech delay in 6-year-old children is 3.8% and 1.5 times more prevalent in boys (4.5%) than girls (3.1%) with the comorbidity of speech delay and language impairment 1.3% and 0.51% if that language impairment was specific, that is, nonverbal intellect was in the normal range: looked at alternatively, approximately 5–8% of children with persisting specific language impairment (SLI) have speech delay (Shriberg et al. 1999). There is an association of intellectual impairment in persisting speech and language delays in 50% of girls and 20% of boys at kindergarten stage.

The prevalence of primary specific speech and language disorders varies according to the discrepancy criteria employed and age group examined (Law et al. 2000). When defined by a
### Table 31.2  ICD-10 classification of speech, language and communication disorders

<table>
<thead>
<tr>
<th>Code</th>
<th>Disorder Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F80</td>
<td>Specific disorders of speech and language</td>
<td>Disorders in which normal patterns of language acquisition are disturbed from early stages of development. The conditions are not directly attributable to neurological or speech mechanism abnormalities, sensory impairments, mental retardation or environmental factors. Specific developmental disorders of speech and language are often followed by associated problems such as difficulties in reading and spelling, abnormalities in interpersonal relationships as well as emotional and behavioural disorders.</td>
</tr>
<tr>
<td>F80.0</td>
<td>Specific speech articulation disorder</td>
<td>A specific developmental disorder in which the child’s use of speech sounds is below the appropriate level for mental age but in which there is a normal level of language skills. Developmental: Phonological disorder Speech articulation disorder Dyslalia Functional speech articulation disorder Lalling Excl: speech articulation impairment (due to): Aphasia NOS (R47.0) Apraxia (R48.2) Hearing loss (H90–H91) Mental retardation (F70–F79) With language developmental disorder: Expressive (F80.1) Receptive (F80.2)</td>
</tr>
<tr>
<td>F80.1</td>
<td>Expressive language disorder</td>
<td>A specific developmental disorder in which the child’s ability to use expressive spoken language is markedly below the appropriate level for mental age but in which language comprehension is within normal limits. There may or may not be abnormalities in articulation. Developmental dysphasia or aphasia, expressive type Excl: acquired aphasia with epilepsy [Landau-Kleffner] (F80.3) Dysphasia and aphasia: Not otherwise specified (NOS) (R47.0) Developmental, receptive type (F80.2) Elective mutism (F94.0) Mental retardation (F70–F79) Pervasive developmental disorders (F84.–)</td>
</tr>
<tr>
<td>F80.2</td>
<td>Receptive language disorder</td>
<td>A specific developmental disorder in which the child’s understanding of language is below the appropriate level for mental age. In virtually all cases expressive language will also be markedly affected, with abnormalities in word-sound production common. Congenital auditory imperceptions Developmental: Dysphasia or aphasia, receptive type Wernicke aphasia Word deafness Excl: acquired aphasia with epilepsy (Landau-Kleffner) (F80.3) Autism (F84.0–F84.1) Dysphasia and aphasia: NOS (R47.0) Developmental, expressive type (F80.1) Elective mutism (F94.0) Language delay due to deafness (H90–H91) Mental retardation (F70–F79)</td>
</tr>
</tbody>
</table>

*Continued*
**SPEECH PRODUCTION**

Most children who present with problems in speech production have difficulties with their phonological system. Speech is a phonemic system in which groups of sounds are combined to convey meaning with the phonological component of speech having rules of contrast (the sound system) and sequence (sound structure). By 6 months of age infants can make most of the 46 phonemes required for the English language, however, speech is a highly complex skill involving rapid, precise and accurate movements of the organs of articulation. Speech production requires integrity of multiple systems including phonological (cognitive and linguistic), articulatory (sensory-motor), praxic (planning/programming of spatiotemporal parameters of movements of the articulators for speech) and prosodic (stress, intonation and voice quality conveying meaning and affect). The anteriorly articulated consonants ‘p, b, t, d’ are the phonemes mastered quickest, followed by ‘k and g’. The posteriorly articulated consonants are a later developmental phenomena so that during normal speech development one sees common substitutions for example, ‘t for k’, ‘d’ for ‘g’. The later acquired consonants ‘r, l, s, th, ch, y and z’ are more difficult to articulate and give rise to classic developmental omissions, substitutions and reversals in speech (McLeod and Bleile 2003).

There is a wide range of normal for the onset of speech, with the 97th centile for single words being 20 months for girls and 23 months for boys, with the 97th centile for three to four word sentences being 3 years for both boys and girls. Table 31.3 illustrates the normal milestones of speech sounds and language comprehension.

A summary of expected progress in a typical phonemic language would encompass syllabic babble for example, ‘ba, da’ characteristic of infants of 6–7 months, with the development of two to three words with meaning at the age of 1 year to two to three word combinations at the age of 21–24 months. There is a rapid increase of up to 500 items of vocabulary during the 6 months after onset of word combinations in typically developing children (Gale et al. 2013).

A rough guide to the mean length of utterance for typically developing children can be calculated from the child’s age in years +1, with an average 3-year-old having a mean length of utterance in their sentences of four morphemes as well as girls and first-born children showing significant advantages in using sentences. Intelligibility improves with improving speech pronunciation and there is a rule of fours with respect to intelligibility: divide a child’s age into four and the quotient is approximately equal to the amount of speech that should be understandable, with a 1-year-old 25% of the time, the 2-year-old 50% of the time, a 3-year-old 75% of the time and a 4-year-old close to 100% of the time (Coplan 1985). This development can be measured between 16–30 months by ‘communication development inventories’, for example, MacArthur Communicative Development Inventory (Fenson et al. 1993) and the UK SureStart Language Measures (2005). They are most accurate when language skills are emergent rather than when relying on recall (Law and Roy 2008).

Speech and language therapists/pathologists have a wide range of standardised validated measures to establish the level of a child’s speech and language development (McCauley 2001; McCormack et al. 2012) as well as outcome measures that assess impact on daily life (McCormack et al. 2010).
LANGUAGE

Language comprehension and spoken word recognition is a very complex process in which the child has to handle the auditory information and assess it against knowledge of sounds in their language to achieve meaning. There is the potential for this to break down at many levels with poor auditory language comprehension possibly resulting from problems in the basic acoustic processing, a difficulty with a fully developed knowledge of speech sounds (phonological processing), abnormal word level knowledge (lexical processing) and/or deficits processing meaning (semantics). Difficulties with spoken word recognition are a hallmark of SLI (Malins et al. 2013).

The critical underlying deficits in SLI are still debated (Bishop 2006, 2016). Some children are reported to have a deficit specific to the domain of language such as in the grammar component, whereas for others there is opposing evidence to suggest it is primarily a processing deficit and in particular a temporal auditory processing problem (Tallal et al. 1993) or that the deficit is underpinned by generic cognitive difficulties resulting in reduced capacity and processing of procedural memory (Boyle 2010). These underpinnings may not be mutually exclusive.

The type of language impairment relates to the form of these generic cognitive difficulties. There is some evidence that verbal and visual short-term memory, (i.e. immediate short-term storage and recall of untransformed information) as well as working memory (i.e. where there has been further processing of the material to be remembered) function in different ways depending on whether the language disorder involves expressive language only or is mixed and also involves receptive language or understanding. The verbal memory appears to be more affected for children who have expressive language impairment whereas for children who have both receptive and expressive difficulties there is involvement of both visual and verbal short-term as well as working memory (Baird et al. 2010).

In very young children the differential diagnosis between specific receptive language impairment and ASD can be challenging (see Chapter 29). Some features such as echolalia, while commonly seen in the preschool child with ASD, also feature in receptive language difficulties. An important clue to ASD is language regression in the second year of life (Baird et al. 2008). Any child presenting with lack of speech/language development should be assessed with both disorders in mind (SIGN 2007; O’Hare 2009a; NICE 2011; O’Hare and Bremner 2016) (see Chapter 29).

Neural Basis

Electrophysiological and haemodynamic imaging studies indicate that normal language functions develop and become established in the child’s brain in a similar pattern to

<table>
<thead>
<tr>
<th>Age</th>
<th>Expected speech sounds and processes</th>
<th>Language comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>Requires to different tones of voice</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>Knows own name as well as the meaning of ‘no’ and several other words</td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>Able to select an object on verbal request, point to body parts and follow simple commands in context</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>Omitting of final consonants e.g. ‘tap’ -&gt; ‘tar’</td>
<td>Can follow commands containing two key ideas</td>
</tr>
<tr>
<td></td>
<td>Consonant harmony e.g. ‘dog’ -&gt; ‘gog’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduplication process e.g. ‘bottle’ -&gt; ‘bobo’</td>
<td></td>
</tr>
<tr>
<td>2½ years</td>
<td>The addition of w:</td>
<td>Can identify everyday objects by their use and enjoy</td>
</tr>
<tr>
<td></td>
<td>Consonant harmony e.g. ‘duck’ -&gt; ‘guk’ should be resolving</td>
<td>simple familiar stories</td>
</tr>
<tr>
<td></td>
<td>although ends of words may still be omitted</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>s, z, f;</td>
<td>Can begin to understand longer and more complex</td>
</tr>
<tr>
<td></td>
<td>Processes of fronting e.g. ‘car’ -&gt; ‘tar’</td>
<td>sentences as well as understand past tense and some</td>
</tr>
<tr>
<td></td>
<td>Consonant blends are reduced ‘spoon’ -&gt; ‘poon’</td>
<td>simple time words</td>
</tr>
<tr>
<td></td>
<td>Some other sounds are emerging e.g. k, g, sh, ch</td>
<td></td>
</tr>
<tr>
<td>3½ years–4 years</td>
<td>Most sounds are now heard but emerging ones do include</td>
<td>Can follow instructions with three verbal concepts</td>
</tr>
<tr>
<td></td>
<td>k, g, sh, ch, j, r, y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Processes include fronting e.g. ‘cat’ -&gt; ‘tat’</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>Most sounds are correct</td>
<td>Can understand most everyday conversations unless</td>
</tr>
<tr>
<td></td>
<td>Some processes are still evident ‘th’ -&gt; ‘f’ e.g. ‘thank you’ becomes ‘fank you’ and ‘rabbit’ becomes ‘wabbit’</td>
<td>very ambiguous</td>
</tr>
<tr>
<td>5½–7 years</td>
<td>Some ongoing speech sound difficulties with ‘r’ and ‘th’ may be ongoing</td>
<td>Can understand implied meaning in language such as</td>
</tr>
<tr>
<td></td>
<td></td>
<td>jokes and puns</td>
</tr>
</tbody>
</table>

Reproduced with permission from British Paediatric Neurology Association Distance Learning Programme.
those of adults (Leroy et al. 2011; Brauer et al. 2013). The expected lateralisation is identifiable at birth, with progression of phonological processing ability during the first months, semantic processing at 12 months and syntactic processing around 30 months. Children with language impairment display functional abnormalities accompanied by structural abnormalities in the inferior frontal and temporal brain regions (Friederici 2006).

Evoked response studies in children also support that the neural basis of language in children is similar to adults (Duffy et al. 2013), reflected by the n400 linking the lexical semantic process with the middle and superior temporal gyri as well as possibly the left inferior frontal gyrus. The syntactic processes (which have been shown in adults to rely on the left superior temporal gyrus in anterior and posterior portion mainly and the left inferior frontal gyrus) and the prosodic processes (which rely on the superior temporal and frontal opercular cortex of the right hemisphere), while appearing to change in their latency and duration in childhood, do not alter in their basic morphology during development from childhood to adulthood.

The mismatch negativity (MMN) component of auditory event related potentials (ERPs) indexes the automatic neuro-physiologic response to sound discrimination and experience dependent central sensory representations of speech sounds in the human brain. MMN provides a link between fine-tuned perceptual abilities and the physiological processes of preconscious stimulus processing correlating with perceptual sound discrimination. Jansson-Verkasalo et al. (2004) used this technique to demonstrate that very low birthweight preterm children have a difficulty in discriminating changes in syllables in a pre-attentive manner which correlates with their sustained naming difficulty in any impaired language development.

Neuropsychological mismatch negativity investigation also reveals early differences in infants from families at high risk of SLI in support of delayed brain responses for the discrimination of syllables, even from the age of 2 months. The children also show later ERP patterns for lexical semantic processes that differ from their age matched controls.

There has also been some support for the deficits in phonological and lexical semantic processes with functional MRI (Hugdahl et al. 2004). Abnormalities in the temporal orbitofrontal dorsolateral and medial frontal cortex and inferior frontal regions have been reported in children with SLI. Leonard (2002) also described reduced left asymmetry in the planum temporale for children with SLI, a region involved in the segregation and identification of sound patterns in speech as well as other acoustic patterns containing specto-temporal information in adults.

The two hemispheres also appear to be differentially specialised in auditory language comprehension in their processing of segmental and suprasegmental features of language. Syntactic and lexical semantic information (segmental) is predominantly assigned to the left hemisphere and prosodic accentuation while boundary marking (suprasegmental) involves the right hemisphere. The speech processing streams in the left and right hemispheres appear to communicate through the posterior portion of the corpus callosum underpinning the neural basis for the coordination and integration of local syntactic and prosodic features during auditory speech comprehension (Sammler et al. 2010).

Connectivity in the brain subserving language can be demonstrated early in life and relates to patterns seen in the fully developed brain. Language comprehension and production both involve cortical pathways with intrahemispheric topographical connectivity between specialised frontotemporal and parietal areas important for language via white matter fibre bundles such as the arcuate superior longitudinal or uncinate fasciculi in the left or right hemispheres. There are important interhemispheric pathways to link the right hemisphere language functions (which include processing of pragmatic and prosodic aspects) with the left hemisphere.

These basic components of the neural language substrate involving inferior frontal and temporal cortices interconnected across hemispheres are present in the newborn and demonstrated in 2-day-old infants with fMRI and diffusion tensor imaging. These basic components of the neural language substrate involving inferior frontal and temporal cortices interconnected across hemispheres will still require further development of functional connectivity and maturation of the intrahemispheric fibre bundles in order to arrive at a highly specialised language system that can manage the lexical and syntactic complexity of the developed brain. There are two fibre connections that link the inferior frontal and temporal language regions in the human brain and the ventral connection that associates the temporal area to the inferior frontal gyrus is already in place at birth, while the dorsal pathway from the temporal cortex to the premotor cortex is also observable at this early age. However, the dorsal pathway to the inferior frontal gyrus matures at a later stage in development and might play a role in more complex language functions (Brauer et al. 2013).

Perani (2011) suggests that in developmental language disorders there may be a disconnection of the language relevant brain regions and a consequent lack of proper functional connectivity during brain maturation.

GENETICS

Primary speech and language impairments have a strong genetic background supported by a family history of late talking predicting ‘late talking toddlers’ (Zubrick et al. 2007) and twin studies (Dale et al. 1998). However, the genetic component is heterogeneous and multifaceted with several linkage regions and genes identified, including on chromosome 16q and 19q (SLI Consortium 2004; Newbury et al. 2005; Bishop 2006; Abrahams et al. 2007). One such common variant is in the Exon 13–15 region of CNTNAP2 which
appears to influence early language acquisition when assessed at the age of 2 years in a general population: CNTNAP2 variants may also increase susceptibility to SLI or autism when occurring together with other risk factors. A language endotype, the nonsense word repetition task (considered to be a measure of phonological working memory and a heritable behavioural marker of SLI (Newbury and Monaco 2002; Newbury et al. 2005) is associated with CNTNAP2 polymorphisms involving a gene that encodes a neurexin expressed in the developing human cortex (Vernes et al. 2008; Whitehouse et al. 2011). These are neuronal transmembrane proteins involved in cell adhesion and have enriched expression in the language related circuits of the brain (Abrahams et al. 2007). The gene is regulated by FOXP2 which is a transcription factor mutated in a very rare monogenic form of speech and language disorder described in the so-called ‘K family’ (Fisher et al. 1998; Fisher and Scharff 2009). Despite these advances in the genetic understanding of language impairment the multifactorial polygenic transmission is not amenable to clinical investigation at present, however, genetic investigations should be considered in some presentations that appear primary and will of course be indicated in many of the secondary causes. The phenotypes of some of the sex aneuploidies including Klinefelter syndrome and XXX and XYY may overlap with that of primary SLI and require investigation (Leggett et al. 2010; Bishop and Searif 2011; Lee et al. 2012). (Table 31.4) Microarray analysis is also recommended as a first line test in all children with velopharyngeal insufficiency where there may be hyper or hypo nasal phonation with up to a third of children affected by 22q11 deletion (Burnell et al. 2014; Ockeleon et al. 2014).

### Table 31.4 Syndromes of sex aneuploidy and language phenotype

<table>
<thead>
<tr>
<th>Sex aneuploidy</th>
<th>Language phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>47 XYY primary non-disjunction of the Y chromosome, 10% mosaics,</td>
<td>Speech and language difficulties are common but fairly diverse and can include speech disfluency, word finding difficulties, problems with expressive language in terms of giving a narrative and difficulty understanding complex sentence structures. Auditory memory problems are also common and most of the children have reading difficulties. The IQ is only slightly below the population mean and is even compatible with an IQ in the superior range. Specific expressive speech and language deficits with problems with word retrieval, syntax and giving narratives accompanied by underlying deficits in auditory processing and short-term auditory memory. The verbal IQ is usually intellectually less than the performance IQ. The child may also be quite socially unresponsive and tend to withdraw from group activities. The majority have expressive language delay which can be severe and there may be a poorer short-term auditory memory. Verbal skills are usually not considered impaired except for problems with verbal fluency but the behavioural profile can include some difficulties in peer relationships.</td>
</tr>
<tr>
<td>46 X/47 XYY with an incidence of one per thousand male live births</td>
<td></td>
</tr>
</tbody>
</table>

### VERBAL DYSPRAXIA

Childhood apraxia of speech or verbal dyspraxia is a severe intractable impairment of speech production that disrupts intelligibility (Morgan and Vogel 2009). Children with verbal dyspraxia appear to have difficulties with precision and patterns of movements underlying their speech production with errors inconsistent and including impaired co-articulatory transitions between sounds and syllables as well as unusual prosody. They have no weakness on a formal examination of the oromotor muscles and their involuntary motor function in chewing, biting and feeding is spared (Morgan and Vogel 2009). It is thought childhood apraxia of speech is a speech motor programming abnormality but effects can be widespread and some consider it to be a more complex linguistically influenced disorder. The boundaries between it and a very severe phonological disorder of speech can be difficult to establish on purely clinical grounds and it may be the better progress of the latter that confers a retrospective diagnostic confirmation.

Some children display almost some degree of spastic dysarthria conferring hypernasality and impaired laryngeal quality resulting in difficulties modulating pitch and loudness. Childhood apraxia of speech is usually associated with receptive and expressive language disorder and reading as well as spelling impairments but verbal skills may be generally poorer than nonverbal skills and some individuals have average nonverbal skills. Hurst (1990) described an extended family with a severe form of verbal apraxia and subsequent study has shown that these affected individuals have a range of difficulties involving processing of phonology and syntax as well as nonlinguistic oral praxis. Imaging abnormalities have been confirmed in speech and language areas in the temporal and
DYSARTHRIA IN SYNDROMIC CONDITIONS

Developmental dysarthria arises secondary to bilateral perisylvian or perirolandic anomalies of polymicrogyria and schizencephaly, vermal anomalies including agenesis, atrophy or hypoplasia of the cerebellum and as part of a Joubert syndrome. The dysarthria is usually severe (Liegeois and Morgan 2012) and these conditions can also be associated with childhood apraxia of speech. An important differential diagnosis from childhood apraxia of speech is Worster-Drought syndrome, sometimes termed congenital suprabulbar paresis, a permanent movement disorder of the bulbar muscles. There are swallowing, feeding, speech and saliva control impairments, the bulbar dysfunction is severe and persistent and there is poor speech prognosis (Clark et al. 2010). The clinical syndrome of Worster-Drought, characterised by bulbar cerebral palsy and a mild spastic tetraplegia, can be associated with bilateral or unilateral perisylvian polymicrogyria but alternatively these imaging abnormalities can be present without the clinical syndrome of the bulbar involvement. Children who have the imaging abnormality do appear to have a high risk of epilepsy and regression and there may be considerable impairment as over half of the children in this large series of those with bulbar cerebral palsy and perisylvian polymicrogyria had no speech (Clark et al. 2010). Dysarthria also arises secondary to brainstem dysgenesis which has been described as accompanied by congenital hypotonia, multiple cranial nerve involvement and oculomotor apraxia (Roig et al. 2003).

INTERVENTION

Late talkers between 24 and 30 months may respond to a range of direct and indirect speech as well as language therapy interventions by increasing their vocabulary and mean length of utterances (Buschman et al. 2009; Allen and Marshall 2011; Cable and Domsch 2011; Yoder et al. 2011; Fricke et al. 2013). Both therapy given directly by speech and language therapist/pathologist or indirectly by education or clinical staff under their direction can be effective for school-aged children with expressive language impairment (Boyle et al. 2007; Boyle 2010; Boyle et al. 2010). Receptive language skills in this age group are less responsive to therapy (Law et al. 2003) although it may support skills underpinning reading comprehension (Fricke et al. 2013).

The current evidence base for intervention for children with primary speech and language delay or disorder is assembled within the ‘What Works’ database hosted by the UK Communication Trust (www.thecommunicationtrust.org.uk/whatworks). This is a searchable and interactive database designed for use by practitioners such as speech and language therapists/pathologists as well as educational psychologists and specialist teachers and integrates information that has been distilled from the Cochrane Collaboration Systematic Review on Speech and language therapy interventions along with practitioner and parental feedback on current practice. The information is grouped into target groups, for example, speech, language, communication along with the age range, what kind of intervention is the focus, who it is to be delivered by and how it is to be delivered (Law et al. 2015).

Some of the severe speech production problems such as childhood apraxia of speech and Worster-Drought syndrome are seemingly intractable with a poor evidence base for treatment efficacy (Morgan and Vogel 2009) so intelligibility remains poor and augmentative alternative communication may be indicated (Baxter et al. 2012).

PROGNOSIS

Around half of children with previously delayed speech and language development will have shown substantial catch up at the age of 3–5 years (Johnson et al. 1999; Law et al. 2000) although they may still have a reduced mean length of utterance despite having developed normal vocabulary, with children who have an underlying receptive language delay more likely to have persisting problems. In a large general population cohort, early language ability measured with expressive vocabulary at 2 years and receptive language at the age of 4 years, both made a moderate but important contribution to emotional and behavioural functioning at 6 years of age. Some biological risk factors such as the child’s sex, maternal smoking in the first 3 months of pregnancy, birth weight, as well as social risks including the father’s occupation and mother’s level of education also play a role in behavioural difficulties at the age of 6 years. Performance IQ was protective as were maternal characteristics such as knowledge of child development and maternal language and literacy skills (Clegg et al. 2015). There is a variable long-term pattern to nonverbal IQ for children with a history of SLI, with some children showing a fall continuing into adolescence (Botting 2005).

The long-term outcome for some children with persisting speech and language impairment can also be poor when there is associated reduction in academic achievement, an increase in emotional and behavioural difficulties and reduced prospects for employment and training (Reilly et al. 2010). Language skills are frequently strongly associated with literacy difficulties, both of which are predictive for educational attainment even after
controlling for IQ and maternal education (Conti-Ramsden et al. 2009). Affected children may have high rates of emotional, behavioural and attentional symptoms (Yew 2013).

Adolescents with SLI educated in specialist language units may continue to experience impaired peer interaction (Conti-Ramsden et al. 2009; Mok et al. 2014). Adults with a history of receptive developmental language disorder have significant impairments in ‘theory of mind’ skills, that is, the ability to impute the thoughts of others, verbal short-term memory and phonological processing resulting in substantial difficulties with social adaptation and an increased risk of psychiatric disorder (Clegg et al. 2005).

ACQUIRED DISORDERS OF SPEECH AND LANGUAGE

A wide range of insults to the brain result in acquired disorders of language: aphasia and dysphasia and/or speech, dyspraxia, anarthria and dysarthria often with dysphonia and dysfluency (O’Hare 2016). Severe receptive aphasia can be difficult to distinguish from auditory agnosia where comprehension difficulties extend to non speech sounds.

Mutism is an early feature in non-fluent aphasia although fluent aphasia can less, commonly occur. The long-term outcome depends on timing, the location and extent of the lesion, specificity of the underlying neural substrate and age of the child (Stiles 2000; Johnson 2008). While young children appear to recover more effectively from aphasia than adults, with the concept of plasticity evoked to explain this, greater sophistication of imaging and assessment of functional outcomes confirm that the long-term effects are potentially widespread and impairing, particularly for infants.

There is an increasingly evidenced literature for the treatment of dysarthria, mostly for children with cerebral palsy. The evidence base for therapy and interventions in childhood aphasia is poorly developed beyond individual and case series and is in the domain of the speech and language therapist/pathologist so is not discussed in detail. There is, however, often a role for augmentative and alternative communication, particularly in the acute management of expressive aphasia and longer term when dysarthria severely disrupts speech intelligibility, with this covered as and when appropriate.

DYSARTHRIA

Dysarthria is an impairment of speech articulation that reduces speech intelligibility, particularly through effect on consonant production but also a range of additional impacts on phonation, resonation and prosody. Speech can sound slurred and effortful and there may be associated dysphagia as well so the clinical assessment of the integrity of the airway protection is crucial.

Dysarthria is a long-term and severe speech disorder of neuromuscular control of speech sound production and signals bilateral disruption of neural pathways (Ligeois and Morgan 2012; Morgan et al. 2013). It is associated with lesions in the white matter along the cortico bulbar and spinal tracts (incorporating corona radiata, central semiovale, internal capsule), midbrain, grey matter lesions within the persylvian and peri rolandic cortices, basal ganglia of putamen, caudate nucleus, thalamus and cerebellum. The best predictor of an outcome of dysarthria is involvement of the dorsal corticobulbar tract.

Dysarthria affects around one third of children with cerebral palsy (Pennington et al. 2013), 20% of survivors of moderate to severe traumatic brain injury (Morgan et al. 2010) and a third of children who have undergone resection of a neoplasm in the posterior fossa (Mei and Morgan 2011; see also Chapters 8, 13 and 14).

Table 31.5 separates dysarthria into flaccid, that is, lower motor neurone bulbar palsy, spastic dysarthria (pseudo bulbar palsy), extrapyramidal where involuntary movements interfere with articulation and ataxic dysarthria where dysfluency is prominent.

Figure 31.2 shows features of cerebellitis that gave rise to an ataxic dysarthria.

Dysarthria is an abnormality of the pitch and volume of the voice resulting in hoarseness and reduced voice volume. Voice disorders essentially arise from two broad groups of disorders, anatomical and neurological, with the former including changes to the larynx and vocal cords which may be acute following infectious causes such as laryngitis and conditions including a laryngeal web, papillomata, granulomas, vocal chord palsy, tumours or endocrine aetiologies such as hypothyroidism. Sometimes the disorder can be attributed to vocal abuse and misuse which can be occurring in combination with vocal nodules (Gale et al. 2013) while neurological causes include damage to the superior and recurrent laryngeal nerves, myasthenia gravis, brainstem haemorrhage and pontine gliomas. Occasionally it can have a psychogenic aetiology (Gale et al. 2013).
hypoglossal nerve dysfunction with reduced tongue strength and coordination, while there may also be trigeminal nerve impairment affecting jaw movements and vagus nerve involvement that impairs velopharyngeal function, all of which conspire to reduce intelligibility. Ten per cent of children in one series of those sustaining moderate to severe traumatic brain injury had accompanying dysphagia (Morgan et al. 2010).

**Posterior Fossa Syndrome**

Eight per cent of children develop the classic picture of ‘posterior fossa syndrome’ after tumour resection in the posterior fossa characterised by cerebellar dysfunction, oculomotor dyspraxia, oral motor dyspraxia, emotional lability and mutism. Up to a third of children overall will experience dysarthria in the acute postoperative phase with recovering speech showing deficits that include distorted vowels, slow rate, voice tremor and monopitch, features that differ from those found in adult onset ataxic dysarthria (De Smet et al. 2012). While the postoperative mutism is associated with a poorer long-term prognosis with long-term dysarthria even non-mute children experience long-term speech deficits of mild dysarthria affecting consonant production, pitch and rate (Morgan et al. 2011).

**Rarer Causes of Acquired Dysarthria**

Herpes virus infections of the brain have a predilection for the temporal lobes and can have a devastating encephalitis presentation. However, the neurological manifestations in

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**Table 31.5 Types of dysarthria with clinical features and aetiologies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical features</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaccid dysarthria (lower motor neurone lesion)</td>
<td>Lax open mouth</td>
<td>Dystrophia myotonica</td>
</tr>
<tr>
<td></td>
<td>Atonia</td>
<td>Prader Willi Syndrome</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td></td>
<td>Wasting</td>
<td>Facio-scapulo-humeral dystrophy</td>
</tr>
<tr>
<td></td>
<td>Drooling</td>
<td>Congenital dysplasia of the brainstem (Moebius)</td>
</tr>
<tr>
<td></td>
<td>Feeding difficulties</td>
<td>Pontine gliomas</td>
</tr>
<tr>
<td></td>
<td>Absent jaw, gag and cough reflex</td>
<td>Progressive motor neurone disease e.g. Fazio-Londe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular lesions of the brainstem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior fossa tumour resection</td>
</tr>
<tr>
<td>Spastic dysarthria (upper motor neuron)</td>
<td>Release of brainstem reflexes</td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td></td>
<td>Stiff jaw</td>
<td>Degenerative brain disease e.g. Battens (can also be characterised by a clustering which is a dysrhythmia of the speech)</td>
</tr>
<tr>
<td></td>
<td>Difficult to open mouth</td>
<td>Metachromatic leukodystrophy</td>
</tr>
<tr>
<td></td>
<td>Brisk jaw jerk with clonus</td>
<td>Acquired traumatic brain injury</td>
</tr>
<tr>
<td></td>
<td>Small bunched tongue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid tongue movements are difficult</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gag and cough reflex present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No wasting</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Many unwanted movements that interfere with normal articulation</td>
<td>Kernicterus</td>
</tr>
<tr>
<td></td>
<td>Retention of obligatory feeding reflexes</td>
<td>Hyponic ischaemic brain injury</td>
</tr>
<tr>
<td></td>
<td>Gag and cough reflex retained</td>
<td>Degenerative diseases of the basal ganglia</td>
</tr>
<tr>
<td>Ataxic dysarthria (cerebellum)</td>
<td>Gag and cough reflex retained</td>
<td>Congenital abnormalities of cerebellum</td>
</tr>
<tr>
<td></td>
<td>Disrupted rhythm and volume control</td>
<td>Posterior fossa resections</td>
</tr>
<tr>
<td></td>
<td>Verbal dyspraxia features</td>
<td>Syndromic example Jouberts syndrome</td>
</tr>
<tr>
<td></td>
<td>Slow development of speech articulation</td>
<td>Post-acquired cerebellar disorders</td>
</tr>
</tbody>
</table>

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Part XII  Developmental and Neuropsychiatric Disorders of Childhood

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childhood can also rarely include opercular syndrome with facial palsy, dysarthria and dysphasia. These conditions constitute a medical emergency requiring urgent treatment with high dose intravenous acyclovir and so the second, slightly more unusual, presentation needs to be recognised as a herpes virus brain infection (Britton and Jones 2014).

There is a small number of reports in which dysarthria is associated with metabolic disorder (Liegeois and Morgan 2012). In contrast to adult practice dysarthria resulting from basal ganglia dysfunction is very rare but seen in juvenile Huntingdon’s chorea and pantothenate kinase associated neurodegeneration. Dysarthria can result from white matter impairment across the cerebral hemispheres in leukodystrophies and, with disease of the cerebellum and basal ganglia, in gangliosidosis and Wilson’s disease.

Onset dysarthria may arise from treatable conditions such as some of the rare motor neuron diseases of childhood, for example, Brown-Vialetto-Van-Laere syndrome and Fazio-Londe syndrome where riboflavin may slow down the degenerative process. Timely diagnosis is also important because there can be rapid progression of wider neurological features after the disease onset: for example, Fazio-Londe syndrome can manifest with onset dysarthria and the child may then show rapid progression with stridor, respiratory distress, prosis as well as facial and limb weakness over the ensuing 16–18-month period. Investigation including neurophysiology and electromyography confirms anterior horn cell involvement in the cranial nerve nuclei and spinal cord (Spagnoli and de Sousa 2012).

**APHASIA/DYSPHASIA AND AUDITORY AGNOSIA**

Aphasia/dysphasia are terms only now usually used in relation to acquired disruption of language function which may be expressive or mixed receptive/expressive and fluent or non-fluent. Aphasia is frequently comorbid with dysarthria and dyspraxia especially if the insult to the brain was diffuse: there is a wide range of causes including acquired brain injury from trauma, cerebral vascular events and stroke as well as infection, for example, herpes simplex encephalitis, temporal lobe abscess and cortical thrombophlebitis, tumours and neurodegenerative diseases such as Niemann Pick disease and adrenoleukodystrophy (Paquier and van Dongen 1996). The latter may involve auditory agnosia.

Figure 31.3 shows acute changes in the left parietal temporal region in keeping with encephalitic process with acute changes of cortical thickening, high signal on T2 weighted imaging and restricted diffusion on diffusion weighted imaging.

A sudden onset of loss of speech which looks like non-fluent aphasia, without other clinical clues to the aetiology such as motor loss or encephalitic symptoms or impaired consciousness, should trigger consideration that this might be selective mutism (Standart and le Couteur 2003), deafness, ASD regression or epileptic aphasia as in Landau-Kleffner syndrome.

Acute fluent aphasia/dysphasia is manifest with telegraphic speech, word finding difficulties, phonemic paraphrases, logorrhoea, semantic jargon, neologistic jargon, that is, scrambled sound structures that result in non words, abnormal speaking rates and impairment of comprehension. The jargon aphasia, paraphasia and perseveration has a similar pattern to that seen in adult aphasics (Van Dongen et al. 2001).

The dysphasia in ‘occult’ and paroxysmal aetiologies, including temporal lobe neoplasms and Landau-Kleffner dysphasia, may be challenging to recognise. Characteristics described in non-fluent and fluent aphasia may not be recognised as such in children who are otherwise considered to be ‘odd’ in their presentation of fluctuating behaviour.
and communication, risking valuable loss of time in these conditions that can be devastating but potentially treatable. Such an example might be herpes simplex encephalitis which may present the classic frontotemporal syndrome of fever, personality and behaviour change. There may be fluctuating aphasia, with or without hallucinations in a minority, while over 90% have nonspecific features (Britton and Jones 2014). The acute phase may be followed by longer term speech production and high level language impairments even though children generally show far greater recovery from acquired aphasia than adults. There can be relative preservation of comprehension in the acute phase and subsequent rapid improvement in speech and expressive language.

Acquired Epileptic Syndromes Associated with Language Regression/Aphasia/Agnosia

Landau-Kleffner syndrome is an epileptic aphasia occurring in childhood (see Chapter 16) which can start insidiously or appear as an auditory agnosia in a child who was previously either developmentally normal or had straightforward developmental delay in speech and language acquisition (Fandino et al. 2011; Deona and Roulet-Perez 2016). It has a peak presentation of between 5–7 years with an age range of 3–10 years with onset difficulty interpreting speech and sometimes environmental sounds and gestures which may be associated with unusual behaviour arising from intense difficulty understanding language and verbal instructions, resulting in a rapid and severe loss in spontaneous speech. While the EEG shows prominent epileptiform activity, there may be no outward signs of seizures meaning that the actual epilepsy may not be recognised although it is a disorder of language associated with such. It is important to record the EEG in drowsiness and sleep as the abnormalities which include classically sharp waves in the bitemporal areas and sometimes frontal dysrhythmias may not be immediately evident in a routine EEG (Fig. 31.4).

This acquired epileptic aphasia is one of the epileptic encephalopathies of childhood and is related to continuous spike wave discharges in non-REM sleep (Deonna and Roulet-Perez 2005). The diagnosis can be delayed as a child might appear deaf or there may be behaviour disturbances and anxiety with the child being unable to understand what is happening and relate their experience. Sometimes when Landau-Kleffner syndrome has been longstanding there can be more of an ASD picture emerging but in the early stages of Landau-Kleffner syndrome there remains a desire to communicate and make social overtures. In contrast, the regression seen typically in the second year of life in ASD is associated with a clear regression in nonverbal communication and reciprocal social interaction.

It is important to think of dysphasia/auditory agnosia arising from an epileptic encephalopathy because although clinical epileptic seizures will ultimately occur in 70–80% of children with Landau-Kleffner syndrome they may not be very evident initially. Auditory agnosia can result from bilateral dysfunction of primary auditory cortical areas with a range of potential aetiologies from vascular, traumatic or infectious including bilateral opercular syndrome with pseudobulbar palsy as an outcome of encephalitis, however Landau-Kleffner syndrome is most likely to be the diagnosis when auditory agnosia appears to arise spontaneously. The diagnosis of Landau-Kleffner syndrome must be considered with repeat EEG study: the EEG abnormalities can be highly variable with interictal epileptiform discharges that are multifocal, bilateral and predominate over the temporal and parietal regions (Van Bogaert et al. 2013; Duffy et al. 2013) (see Chapter 16).
INVESTIGATION
All children have to be thoroughly evaluated by a child neurologist. Cranial imaging is indicated in the investigation of onset dysarthria and dysphasia guided by the context in which these symptoms are occurring, for example, a stroke or cerebral vascular accident, infectious process (Fig. 31.5) or post-traumatic injury. Sleep VEEG is also an important diagnostic investigation.

PROGNOSIS

Dysarthria
There can be a wide variation seen in individual responses to therapy although preliminary investigations suggest that gains in intelligibility and communicative interactions can be demonstrated in young children with dysarthria after brief intensive speech and language therapy (Pennington et al. 2013; Coleman et al. 2015). Overall the evidence base for treatment efficacy is limited (Morgan and Vogel 2008).

Dysphasia
Functional brain imaging studies confirm recovery from aphasia is protracted but ‘dynamic’. The respective roles of the impaired left hemisphere and the greater right hemisphere lateralisation change over time. While right hemisphere lateralisation follows the acquired brain damage in children with cerebral vascular accident and aphasia greater subsequent recovery is seen in those where there is some degree of reorganisation in the left hemisphere (Elkana et al. 2011; Liegeois and Morgan 2012). Proficiency in linguistic tasks and a better prognosis is associated with increasing lateralisation to the left hemisphere in the anterior language regions. Despite significant recovery of aphasia many individuals show persisting dysphasic features characterised by reduced naming and phonetic fluency in spoken and written language (Lauterbach et al. 2010; Elkana et al. 2011): long-term management for these children should include multidisciplinary liaison in conjunction with speech and language therapy/pathology colleagues as well as with education staff so they can remediate the impact of these dysphasic outcomes. This support is likely to be needed long term in some capacity into high school where the child will encounter a huge increase in technical vocabulary.

Traumatic brain injury is associated with poorer outcomes in language related cognitive delays. Impairments in spoken and written language comprehension occur more commonly in children with moderate to severe traumatic brain injury and particularly affects higher cognitive skills such as non-literal language, affecting an ability to make inferences and deal with inferred meanings such as sarcasm and metaphor. This type of language difficulty is linked to problems in working memory, processing speed, social cognition and the child’s executive functioning (Turkstra et al. 2015).

INTERVENTION
Despite the importance of acquired dysarthria and dysphasia for disrupting quality of life there is very little evidence on which to base treatment (Morgan and Vogel 2008), however the increasing understanding of the long-term effects and impact of unintelligible speech and communication effectiveness on activity and participation framed with the ICF should improve the drive for evidence towards meaningful outcomes (Hidecker 2010; Hidecker et al. 2011) (Table 31.6). The Focus on the Outcomes of Communication Under Six (FOCUS) (available at www.focusoutcomemeasurement.com) is such a tool derived from parents descriptions of their children’s communication that complies with the ICF and the ICF – Children

Intervention also needs to build on a detailed assessment of the child’s speech, language and communication for both spoken and written modes as appropriate (Table 31.7). This is the domain of the speech and language therapist/pathologist within a multidisciplinary team which can avoid misconceptions about the breadth of a child’s disabilities. Experienced therapists can evaluate the clinical picture through informal language measures and assess narrative as well as functional communication (McCormack et al. 2012). Children with cerebral palsy and those such as the preterm survivor with periventricular leukomalacia with an intelligence level above 70 but nevertheless significant motor speech problems may respond to conversation rather than start it, seem to avoid elaborating within conversation and seldom ask questions (Pirila et al. 2007): this may result in an underestimation of the child’s comprehension. Commonly used standard language tests for comprehension of spoken language may have limited utility for children with severe cerebral palsy who have no intelligible speech (Geytenbeek et al. 2010) but this may be circumvented to give a true picture of understanding with the appropriate modifications to psychometric instruments or necessitate the development of bespoke instruments to assess comprehension in such children (Geytenbeek et al. 2014, 2015).

**AUGMENTATIVE AND ALTERNATIVE COMMUNICATION**

There should always be appropriate consideration of augmentative and alternative communication (AAC) to allow a child to develop as an independent communicator if severe impairment of speech intelligibility or lack of speech occurs acutely or in the long term. AAC includes unaided modes such as gesture and aided communication modes that can be low technology systems such as photographs and pictograms or high technology systems which include voice output communication aids. People with a disability have a right to access a chosen form of communication but there are a wide range of factors that influence how successful or not the introduction of an AAC device might be. The impact of high technology AAC depends on a whole range of factors as diverse as the availability of technical support, reliability of the device and the sound of the voice output to the individual and family perceptions as well as knowledge and skill of the staff supporting the AAC user (Baxter et al. 2012). Families may need to be reassured that AAC will not prevent the recovery of speech as they can worry that the child becomes dependent on that system. As speech recovers the child will always opt to employ it.

Some children with severe cerebral palsy, particularly of the dyskinetic type who have no language, may nevertheless have well developed language comprehension emphasising the importance of introducing AAC devices from early childhood. Children with spastic cerebral palsy have more severe language comprehension difficulties than children with dyskinetic cerebral palsy: because of the severe motor implications affecting speech and the use of gesture it is important to have methods of evaluating receptive language and not assume that it is severely affected in non-speaking children with severe cerebral palsy (Geytenbeek et al. 2015). It is vitally important to maintain communication and a fundamental component of good quality of life following recovery from these devastating acquired dysarthric and dysphasic conditions.

### Table 31.6 The five levels of the Gross Motor Function Classification System (GMFCS), the Manual Ability Classification System (MACS) and the Communication Function Classification System (CFCS) classification

<table>
<thead>
<tr>
<th>Levels</th>
<th>GMFCS a</th>
<th>MACS b</th>
<th>CFCS c</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Walks without limitations</td>
<td>Handles objects easily and successfully</td>
<td>Sends and receives with familiar and unfamiliar partners effectively and efficiently</td>
</tr>
<tr>
<td>II</td>
<td>Walks with limitations</td>
<td>Handles most objects but with somewhat reduced quality and/or speed of achievement</td>
<td>Sends and receives with familiar and unfamiliar partners but may need extra time</td>
</tr>
<tr>
<td>III</td>
<td>Walks using a hand-held mobility device</td>
<td>Handles objects with difficulty; needs help to prepare and/or modify activities</td>
<td>Sends and receives with familiar partners effectively but not with unfamiliar partners</td>
</tr>
<tr>
<td>IV</td>
<td>Self-mobility with limitations; may use powered mobility</td>
<td>Handles a limited selection of easily managed objects in adapted situations</td>
<td>Inconsistently sends and/or receives even with familiar partners</td>
</tr>
<tr>
<td>V</td>
<td>Transported in a manual wheelchair</td>
<td>Does not handle objects and has severely limited ability to perform even simple actions</td>
<td>Seldomly sends and receives effectively, even with familiar partners</td>
</tr>
</tbody>
</table>

a Palisano et al. (1997), b Eliasson et al. (2006), c Hidecker et al. (2011).
# Table 31.7 Communication problems seen after moderate-severe traumatic brain injury in children and adolescents

<table>
<thead>
<tr>
<th>Aspect of communication</th>
<th>Communication problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Language comprehension</strong></td>
<td>Poor comprehension of vocabulary</td>
</tr>
<tr>
<td></td>
<td>Difficulty remembering instructions or following directions</td>
</tr>
<tr>
<td></td>
<td>Difficulty sequencing or following multiple directions</td>
</tr>
<tr>
<td></td>
<td>Difficulty with the rate, complexity or amount of spoken or written information presented at one time</td>
</tr>
<tr>
<td></td>
<td>Inability to keep up with complex sentences or vocabulary</td>
</tr>
<tr>
<td></td>
<td>Requires additional time to understand what others are saying</td>
</tr>
<tr>
<td></td>
<td>Requests multiple repeats of information</td>
</tr>
<tr>
<td></td>
<td>Slow reading rate</td>
</tr>
<tr>
<td></td>
<td>Problems understanding or recalling what was read</td>
</tr>
<tr>
<td></td>
<td>May not understand puns, sarcasm or humour and may take what is said literally</td>
</tr>
<tr>
<td><strong>Language production</strong></td>
<td>Difficulty identifying the gist of stories and/or important story elements</td>
</tr>
<tr>
<td></td>
<td>Problems in developing and using new vocabulary</td>
</tr>
<tr>
<td></td>
<td>Difficulty remembering desired word when speaking or writing</td>
</tr>
<tr>
<td></td>
<td>Uses ‘thing’ or ‘you know’ rather than the noun or verb</td>
</tr>
<tr>
<td></td>
<td>Problems organising thoughts to say what is on his or her mind</td>
</tr>
<tr>
<td></td>
<td>Slower to respond to written or verbal directions or questions</td>
</tr>
<tr>
<td></td>
<td>Unable to form response to a question in usual time allotted for students to respond, even though he or she might know the correct response or behaviour</td>
</tr>
<tr>
<td></td>
<td>Poor spelling</td>
</tr>
<tr>
<td></td>
<td>Difficulty writing sentences</td>
</tr>
<tr>
<td><strong>Pragmatic communication</strong></td>
<td>Takes turns at inappropriate times or monopolises the conversation</td>
</tr>
<tr>
<td></td>
<td>Talks about unrelated topics</td>
</tr>
<tr>
<td></td>
<td>Interrupts with irrelevant ideas</td>
</tr>
<tr>
<td></td>
<td>Unable to monitor quality of his or her own conversation</td>
</tr>
<tr>
<td></td>
<td>Continues talking when others indicate they are uninterested</td>
</tr>
<tr>
<td></td>
<td>Engages in lengthy, disorganised explanations</td>
</tr>
<tr>
<td></td>
<td>Rambling conversation or written expression</td>
</tr>
<tr>
<td></td>
<td>Minimal responses to questions with an inability to fill in details or offer other supporting information</td>
</tr>
<tr>
<td></td>
<td>Difficulty using language to achieve specific goals, such as giving hints, negotiating or conveying humour or sarcasm</td>
</tr>
</tbody>
</table>

Turkstra (2015), adapted from Savage et al. (2005).

## REFERENCES


Chapter 31 Disorders of Speech, Language and Communication


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Psychogenic Neurological Disorders

Paddy Grattan-Smith

Difficulties over Words

Lessons from the Past

Paul Briquet (1796–1881)
James Paget (1814–1899)
Jean-Martin Charcot (1825–1893)
Sigmund Freud (1856–1939)
Pierre Marie Félix Janet (1859–1947)
The Eclipse of Hysteria
Paediatric Papers

The predicament of the child
The provocation of a psychogenic neurological disorder by minor injury or illness
Controversies over the cause
The difficulty in separating organic disease from psychogenic neurological disorders
Malingering
Treatment of the symptom or the underlying cause?
Treatment difficulties and the tendency of families to seek alternative methods
Prognosis

Frequency and Presentation of Psychogenic Neurological Disorders

The ‘Positive Signs’ of a Psychogenic Neurological Disorder
Abnormalities of Gait
Psychogenic Weakness
Lateralisation of Signs
Positive Babinski Sign and Ankle Clonus
Psychogenic Chorea and Dystonia
The Syndrome of Fixed Dystonia
Causalgia-Dystonia, Post-traumatic Dystonia
Psychogenic Tremor
Psychogenic Palatal Tremor
Palatal Myoclonus
Psychogenic Jerks
Psychogenic Tics
Psychogenic Disorders Affecting the Eyes
Psychogenic Speech/Globus Pharyngeus
Sensory Disorders
‘La Belle Indifference’

Overview of the Signs of a Psychogenic Neurological Disorder
The ‘Apparent Voluntary’ Nature of Psychogenic Signs
Red Flags
What Is the Underlying Cause of a Psychogenic Neurological Disorder?
- ‘Neurobiological’ Theories
- ‘Psychological’ Theories
- Taylor’s Approach
- ‘No Evidence of a Psychological Problem’
- The Impact of Delayed Diagnosis

Psychogenic? Functional? What Is the Correct Name?
- ‘Stress’
- Informing the Child and Family of the Diagnosis
- Hostile Reactions

Treatment of Psychogenic Neurological Disorders

Prognosis
The neurologist seeing a child with a psychogenic neurological disorder (PND) faces two main tasks. The first is to make the diagnosis without undue delay. The second is informing the child and family of the diagnosis in a way that allows the diagnosis to be accepted.

The diagnosis of a PND is sometimes easy, especially in the younger child, but often it is difficult, and sometimes extremely difficult. A careful history and examination, a detailed knowledge of anatomy and rare presentations of neurological disorders, the ability to detect ‘psychogenic’ signs, and an understanding of human behaviour are basic requirements, but making the diagnosis is only the beginning. What is meant by the diagnosis has to be explained in such a way that it will hopefully result in the child making a full recovery, avoiding an entrenchment of the symptoms, and a state of affairs where illness becomes a way of life for the child. As Sir Francis Walshe (1965) observed more than 50 years ago: ‘the measure of accuracy in diagnosis is a measure of the experience of the observer, and upon his having the courage of his convictions when he does diagnose hysteria, for the diagnosis is never popular’.

That the first reaction of many parents to the diagnosis of a PND in their child is disbelief, or immediate rejection of the diagnosis, is to be expected. The diagnosis can come to them as an unprovoked slap in the face. Rather than their child having a neurological disease, the parents and child may understand that they are being told the problem is a mental illness. They may feel that, embedded in the diagnosis, there are suggestions of incompetence or dishonesty in the child, poor parenting, and an abusive atmosphere at home. An approach to this difficulty has been to try to find an ‘acceptable’ word. Far more important than the word used, is the explanation of what is meant by the diagnosis.

DIFFICULTIES OVER WORDS

In Chapter 19, dealing with movement disorders, the obstacles that accompany some words were discussed. These difficulties are multiplied many fold when dealing with PND. In quoting various authors in this chapter, the words they employed will be used, realising that hysteria is now regarded as an unacceptable term. Terms such as hysteria, conversion disorder, psychogenic disorder, symptoms unexplained by organic disease, medically unexplained illness, and functional neurological disorder will be taken as broad terms that have similar meanings, with some differences related to the prevailing concepts at the time the papers were written.

When not making direct quotations from the literature, the term ‘psychogenic’ will be used, realising it has problems. Lewis (1972) observed: ‘The term “psychogenic” is much used, but seldom defined – its meaning is assumed to be self evident’. Here psychogenic is used in the sense of ‘not organic’, or as defined in Webster’s Dictionary emanating from ‘the human soul, spirit or mind’. In dealing with children and their families, the author has found, that ‘stress-related’ is a more useful term. The problems with the words will be discussed below in more detail.

The signs of a PND are much the same in adults and children, and this review will not be limited to papers written by paediatricians or paediatric neurologists. Psychogenic non-epileptic seizures are covered in the Chapter 16 and are not discussed here. Mass hysteria is also not covered, but the reader is directed to the review of Mink (2013).

LESSONS FROM THE PAST

Those who cannot remember the past are condemned to repeat it. —Santayana.

The author’s firm belief is that it is impossible to have any real understanding of the diagnosis and treatment of PNDs without a detailed knowledge of the past. Others share this view (Linden et al. 2013). In the last 150 years waves of enthusiasm for the study of PNDs have been followed by periods of disillusionment, with little interest shown in them, or even a denial of their existence. We are currently in a period of intense interest, particularly in the world of adult neurology.
Teodoro and Edwards (2016) have noted a recent ‘revolution in the approach to functional movement disorders’ (FMD).

A review of the past adult and paediatric literature reveals that many areas of current interest have been examined in the past, and are now being ‘re-discovered’. Examples include the ‘positive signs’ of a PND described by Babinski and others, and famously by Head in 1922. Other examples include the presence of a model for the illness (Shill and Gerber 2006; Pellicciani et al. 2014), which was described by Paget (1873), and Taylor (1986). There is a report of familial psychogenic movement disorders (Stamelou et al. 2013), which does not make reference to the work of Briquet in 1859, who found that girls with a hysterical mother were 12 times more likely to have hysteria than those of non-hysterical parents (Mai and Merskey 1980). There are inevitably many such examples, as the past literature on PNDs is vast and often hidden in obscure places, and may be of little interest to those with ‘neurobiological’ leanings. However, they serve as a reminder that a knowledge of the past is essential in trying to have a full grasp of the complexities of PNDs. This historical review has to be brief, and can only provide a limited outline. It leaps over a story thousands of years old, touching down briefly, and then moving on. The author accepts that with such a large literature and limited space, the selection of material is influenced by his own leanings and biases, but he is not alone in this fault.

In the past terms such as ‘hysteria’ were used for a broad group of patients, including some with problems such as pain or anorexia. This historical review concentrates mainly on descriptions that are relevant to our current conception of what constitutes a PND.

Wilson (1930) observed: ‘Leptosy, rabies and malaria are ancient diseases, but epilepsy and hysteria are older still: are they as old as human nature itself?’ Traditionally a review of the history of PNDs goes back to ancient Egypt and ancient Greece. Given the difficulties in making the diagnosis of a PND with a patient in front of you, making it from descriptions written thousands of years ago in archaic languages, has its limitations. Nevertheless, it seems clear that the ancients regarded the womb as a source of multiple symptoms, some of which would now be regarded as evidence of a PND.

From Plato’s Timaeus (approximately 360BC) comes the following description: ‘The so-called womb or matrix of women. The animal within them is desirous of procreating children and when remaining unfruitful long beyond its proper time, gets discontented and angry, and wandering in every direction through the body, closes up the passages of the breath, and, by obstructing respiration, drives them to extremity, causing all variety of disease.’ It has been suggested that here Plato is not actually talking about a wandering womb, but the psychological consequences of suppressed sexual desire (Adair 1995). Nevertheless standard practice at the time was to regard the problem as ‘organic’ with the aim of treatment to drive the womb back to its natural position. ‘If the uterus had moved upwards, this could be done by placing malodorous and acrid substances near the woman’s mouth and nostrils, while scented ones were placed near her vagina’ (Tasca et al. 2012).

Many women in the ancient Mediterranean world wore amulets and charms to protect them against uterine movement (Adair 1995). The ancients do not appear to have used the word ‘hysteria’. However, for thousands of years dysfunction of the womb was seen as a source of widely varying symptoms, including in particular, difficulties with breathing, and loss of consciousness. When the word ‘hysterical’ first appeared in the English medical literature, it reflected the view of the ancients, describing an ‘organic’ disorder caused by dysfunction of the uterus. ‘For so many writers in the history of hysteria, the womb has become a vast, mysterious and infinitely powerful organ’ (Micale 1989).

Travelling forward nearly 2000 years, little progress had been made. In 1603 Edward Jorden published a book entitled A Briefe Discourse of a Disease Called the Suffocation of the Mother (Brain 1963). This followed a trial the previous year where Elizabeth Jackson had been charged with bewitching a 14-year-old girl named Mary Glover, causing her to have seizures. Jorden had appeared in court and attributed the problem to natural causes, but the jury was convinced by evidence (including from other doctors) of witchcraft, and Jackson was found guilty. The message of Jorden’s book was that such symptoms were not supernatural in origin, but due to problems with the uterus. (The term ‘suffocation of the mother’ referred to a sense of choking caused by uterine dysfunction.) It is sad to reflect on the lack of progress in medicine at that time, with Jorden arguing that it was the uterus and not the devil which was responsible for the symptoms, returning to an error thousands of years old. There was some progress, mainly from the great physicians of that time. Both Willis and Sydenham proposed that it was the brain that was the source of the symptoms of hysteria (Brain 1963; Micale 1989).

Jumping forward to 1861, Thomas Chambers in an article in the British Medical Journal (BMJ), (then 21 years old), began with the following statement. ‘Will you please to forget at once and for all that hysteria is derived from the Greek? … In reality, it has no more to do with the organ of reproduction than it has with any other part of the female body; and it is no truer to say that women are hysterical because they have wombs, than that men are gouty because they have beards’ (Chambers 1861).

Chambers goes on to say that ‘the deficient vitality of which hysteria is a manifestation is in that puzzling part of the circle of life which lies between mind and matter’. In his summary he notes that with hysteria: ‘In some cases the mental, in others the bodily, phenomena predominate’. He discusses a number of cases starting with the story of a 17-year-old girl. She had been ‘in service’ from the age of 12, and had no problems until: ‘She went home for a holiday, having heard of no illness in her family; and found her father in his coffin.’ Subsequently, she developed multiple symptoms including palpitations and emotional instability. She lost her position repeatedly. She presented to Chambers with diffuse pains, and paralysed and extremely painful legs. ‘These symptoms followed a minor illness. Examination convinced Chambers that her problems were ‘distinctly mental’ in origin.
Chambers then outlined his method of treatment for patients when the symptoms seem to be psychogenic in origin, using this girl as a model. The first step was admission to hospital. ‘You will find in practice that, however good your theory of the treatment of hysteria may be, it is much more difficult to carry out and much less effective when the patients are at home, than when you can remove them for a time from their ordinary habits and associations.’ If the patient were rich, an alternative was a holiday away from home. However, this had to be carefully chosen as: ‘Much harm is often done by sending them to travel in Italy.’ In Chambers’ view, the eternal city, Rome, was a particular danger. (Florence was not mentioned.) If the family was neither poor nor rich: ‘One good plan that can sometimes be adopted, to the saving of pride and pocket together, is to negotiate an exchange of patients, where two families in about the same social position are simultaneously afflicted with an hysterical member.’

The reason for getting the patient out of the home was that ‘the patient’s mind, by running in its habitual groove, and being perpetually subjected perhaps to the influences which originated the disease, less readily takes a turn towards health’. In the model proposed by David Taylor (which will be discussed below) this could be seen as an alleviation of a predicament. In addition to a change of scene, Chambers recommended an exercise programme, cold shower-baths (for their bracing effect, in winter preceded by a warm bath), and valerian. The aim of treatment is ‘restoring the control of the mind over the body. A link is dropped and is becoming paralysed for want of use’.

The exercise programme involved progressively increased movement, and used music. ‘Let the patients be exercised in voluntarily obeying specific orders for the direction of the will; moving the limbs to time, at first slowly, and afterwards more rapidly, till at last the culminating point of dancing can be arrived at. This is the perfection of the cure; and when a girl can be got to join a quadrille in the evening, you need not fear a relapse into hysterical paralysis.’

Opponents of Cartesian dualism would be appalled by the frequent use of the mind and body as separate concepts in Chambers’ article. He also talks about the value of ‘Christian charity’ in treating patients, (and urges doctors to take into their own family the children of colleagues who develop hysteria). Nevertheless, his treatment is kind, caring, and compassionate in trying to help a young girl, clearly lost and alone in her grief. It also has much in common with ‘recent advances’ in the treatment of PNDs.

In the English literature between 1840 and 1860, a number of British authors, including Thompson, Laycock, Carpenter and Carter described the importance of emotional disturbance in causing hysterical symptoms (Kane and Carlson 1982). Whereas others felt the emotions acted on a vulnerable person, Carter believed that an undischarged, strong emotion was sufficient to cause hysteria in an otherwise normal person. Carter’s book On the Pathology and Treatment of Hysteria was published in 1853. In this he described primary, secondary and tertiary forms of hysteria. The tertiary form would now be called factitious disorder. ‘Carter writes of girls who bind their limbs with tight ligatures to induce swelling of their joints. Patients may burn their skins with corrosive substances to form ulcerations or place local irritants into their vaginas to create discharges. Two common complications are hemoptysis and hematemesis, the former produced by applying leeches inside the mouth, the latter by swallowing and then vomiting the blood of animals’ (Kane and Carlson 1982). In this tertiary form, Carter believed complex psychological processes are at play. ‘The patient soon finds herself unable to stop thinking of the emotions that produce her paroxysms, and her introspective ideas become automatic. The hysterical increasingly loses her control over her symptoms until finally her illness is completely out of her hands’ (Kane and Carlson 1982).

Old ideas die hard, but sometimes with modifications. If not the uterus, other parts of the female genital tract must be responsible. In 1866 in The Lancet, Baker Brown passionately defended his practice of clitoridectomy in the treatment of hysteria (among other ailments), claiming great success. His views were not shared by his surgical colleagues, and he was soon thereafter expelled from the Obstetrics Society. As late as 1884, Walton writing in the Boston Medical and Surgical Journal (later to become the New England Journal of Medicine), firmly believed that removal of the ovaries had a role in selected patients with hysteria. Displaying the zeal found in so many who insist they have found both the cause and cure of PNDs, Walton stated: ‘In such cases the hysterical symptoms may not only furnish an additional indication for the removal of the source of irritation, but they alone may make life such a burden to the patient as to render the operation not only justifiable but imperative.’

It was not only surgeons who focused on the ovaries. As will be discussed below, ovarian pressure to abort hysterical seizures was a standard procedure in the Salpêtrière during the era of Charcot. It was also used by Tilt and others: ‘It has been possible, in cases published by Romberg and Schulzenberger, to produce the succession of phenomena just described by simply pressing on the ovaries; and I have repeatedly brought on unconsciousness in a nervous patient of mine by pressing the left ovary’ (Tilt 1871).

The half-century commencing with Briquet’s 1859 treatise on hysteria was an incredibly rich period in the discussion of the diagnosis, the cause, and the treatment of PNDs. This time will, therefore, be discussed in some detail.

**PAUL BRIQUET (1796–1881)**

In 1859 Briquet published *Traité Clinique et Therapeutique de l’Hystérie*. This was not translated into English until 1980 and then only in part (Mai and Merskey 1980). Briquet’s Treatise was a monumental clinical and epidemiologic study of 430 patients seen over a ten-year period.

Briquet defined hysteria as a ‘neurosis of the brain in which the observed phenomena consist chiefly of a perturbation of vital activities, which serve as the manifestation of affective
feeling and passions’. He also acknowledged the difficulties with the word ‘hystera’. ‘I shall adopt, therefore, the term hystera because it is the one that has been used at first, because it is the most widely used, because everyone knows it, and finally because I hope that with time it will have lost its etymological value and become quite simply another proper noun like gold, iron, or lead.’ Mai and Merskey note: ‘He quotes Galen favorably. “One must attach little importance to these disputes, considering that physicians have quite enough to do being interested in circumstances associated with hystera, not to amuse themselves by wasting their time in arguing over words.”’

Briquet found that hysteria occurred in women and men, but the ratio was 20 women for every man. One-fifth of Briquet’s cases had an onset before puberty and in the majority the onset was before the age of 20 years. Of 100 hysterical mothers who had 220 daughters, hysteria developed in 124 of the daughters. Briquet compared them to non-hysterical patients and concluded: ‘Persons born of hysterical parents are, because of this fact, 12 times as likely to have hysteria develop as those born of non-hysterical parents.’ He also found a higher incidence of ill-health and mortality among the children of hysterical mothers, with their daughters faring worse than their sons.

Briquet observed: ‘Anything that disturbed the equilibrium of the nervous system could theoretically provoke hysteria. Joy, happiness, and physical and moral pleasure never provoked hysteria, whereas grief, worry and sadness, jealousy, fear, and apprehension most strongly predisposed to hysteria.’ One-third of the children had been ‘habitually maltreated or held constantly in fear or had been directed harshly by their parents’. His hysterical patients exhibited typical symptoms such as seizures, paralysis, and sensory change. The sensory disturbance included pain and anaesthesia which more commonly affected the left side. In general, those influences that calmed the nervous system improved hysteria, and those that excited the nervous system aggravated it. In treatment, he emphasised the importance of an improvement in social circumstances, and the need to minimise the pressures of life.

Briquet found that if the hysteria symptoms had lasted a short time, had left no after-effects, and if the original cause was no longer present, a complete recovery could occur. However, once the symptoms were established, the prognosis was poor: ‘No illness is more difficult to cure than hysteria … half of hysterical women recover only when advancing ageulls their sensitivities. One-quarter never recover or have the illness their entire lives. Some young girls who become hysterical before the age of 12 or 13 years are condemned to a lifetime of suffering, malaise, and sometimes serious illnesses. They may spend a year or more in bed, completely incapacitated. They are always sick, abort easily, or if they go to term, give birth to more hysterics. Some remain ill until an advanced age, become cachectic, thin and irritable, and old before their time, leading but a wretched life for themselves and those around them.’

**JAMES PAGET (1814–1899)**

In 1873 James Paget wrote a series of articles in the Lancet on the ‘Nervous Mimicry of Organic Diseases’. The first of these will be discussed in some detail, not simply because it is beautifully written, but because it reveals that much of what is sometimes presumed to be ‘modern’ thought on PNDs, was already established around 140 years ago. Paget described nervous mimicry as occurring when ‘a nervous disorder produces an imitation or mimicry of organic local disease. In some of these cases the mimicry occurs without any substantial disease whatever; in others it gives features of extreme severity to a disease which, in a normal condition of the nervous system, would be trivial or unfelt’.

Paget continued: ‘Cases of this kind are commonly included under the name Hystera; but in many of them none of the distinctive signs of hysteria are ever observed, and from all of them it is desirable that this name should be abolished. For it is absurdly derived, and, being often used as a term of reproach, is worse than absurd. To call a patient hysterical is taken by many people as meaning that she is silly, or shamming, or could get well if she pleased; and no doubt there are patients of whom some of these things may be fairly said; but in many more, hysteria, especially in the form of an unwilling imitation of organic disease, is a serious affection, making life useless and unhappy and not rarely shortening it.’ From the Greek, Paget suggested, ‘neuromimesis’ as a better word than hysteria.

Paget thanked Reynolds and Anstie who had gone before him, and pointed out that the mimicry of organic disease can be ‘so close as to make diagnosis difficult’. He noted the frequency of a minor injury in provoking an episode. ‘In some the sensibility is always too keen, whether for pain or pleasure. In these the pain of an injury is much more severe than what we may suppose to be the proper average of pain producible by that injury: it lasts longer; outliving all the other consequences of the injury.’ He found ‘a singular readiness to be painfully fatigued by slight exertion’. Paget also observed that neuromimesis can occur in people who do not in any way appear ‘hysterical’. ‘Nothing can be more mischievous than a belief that mimicry of organic disease is to be found only or chiefly in the silly, selfish girls among whom it is commonly supposed that hysteria is rife or an almost natural state. It would be safer for you to believe that you are likely to meet with it among the very good, the very wise, and the most accomplished among women.’

Paget found that whereas people with organic disease tended to get on with life, and as far as possible ignore their symptoms, the reverse applied in those with nervous mimicry. ‘Few patients with real hip-disease or real spinal disease, for instance, think half so much about their ailments as they do whose nervous sytems imitate those diseases.’ He made a famous observation on the ‘will’. ‘A girl who has will enough in other things to rule the house has yet not will enough in regard to her limbs to walk a step with them, though they are as muscular as ever in her life. In will these patients are as those who are colour-blind. They say “I cannot”; it looks like “I will not”; but it is “I cannot will”.’
Paget also observed the common presence of a ‘model’. ‘I think it is to this same weakness of will that we may attribute other things often observed in the worst cases of neuroni-mimetic especially the disposition of the patients to assume symptoms of disease that they have seen or heard of, such as the deformities of diseased joints, the lameness or paralysis associated with spine-disease, and the supposed distinctive pains of cancer. No doubt there is sometimes intentional fraud and lying in these cases; but in many more I think you may be sure that patients do not study the imitation or deliberately determine to practise it. Rather they are, in respect of will, like children, who almost involuntarily imitate diseases …’ Paget believed that this tendency to imitate was present in many people, and had to be controlled by an act of will. ‘I think that many persons, even such as have good nervous systems, must be conscious that it requires effort – that is, a full exercise of will – to avoid these imitations, and to disbelieve or disregard sensations imitative of those endured by others.’

Paget is not convinced that all manifestations of nervous mimicry are psychological in origin. He begins with: ‘If you study nervous mimicry in all the varieties of mental strange-ness that may be associated with it, it may often seem to you an entirely mental disorder, due only to imagination, or to intense attention directed on one place, or to adoption of signs heard of, or, in many cases, to an insanity of the intellect; and it is not easy to find sufficient evidence that it is not so.’ However: ‘I may assure you, that to regard all mimicries of organic diseases as essentially mental errors would be bad pathology and worse practice … in some mimicries it is hard to discern any mental influence at all.’

Paget ends by noting that for many people including himself, it is not possible to mimic the symptoms encountered: ‘among the sane there are many who cannot bring about a mimicry of disease by an effort of imagination or direction of the mind. Among these I am happy to count myself. I have tried many times carefully, and with good opportunities, but have always failed’.

Paget was not alone in having doubts about the cause and nature of hysteria. Bristowe (1885) delivering The Cavendish Lecture observed: ‘I have quoted a series of cases which I have labelled “hystera”, and have compared them with other cases, some of which I have regarded as not hysterical. But what right have I to make this distinction between them? Again, I ask what is hysteria?’

**JEAN-MARTIN CHARCOT (1825–1893)**

Jean-Martin Charcot was a medical colossus, both as a general physician and as a neurologist. Eponyms associated with his name include: maladie de Charcot (motor neuron disease), Charcot–Marie–Tooth disease, Charcot–Erb paresis, Charcot–Joffroy syndrome, Charcot’s artery, Charcot–Bouchard aneurysms, Charcot–Wilbrand syndrome, Charcot’s triad, Charcot–Weiss–Baker syndrome, Charcot’s joint, Charcot–Leyden crystals and Charcot’s biliary fever. Most of his working life was at the Salpêtrière in Paris, where he became superintendent physician in 1862. His patients there were all women who had chronic rheumatological and neurological diseases, at that time regarded as ‘incurable’. Following a French tradition, Charcot applied the *métod e anatomo-clinique* to his patients (Goetz 2010). This consisted of careful initial examination and then close clinical follow-up, followed by a detailed examination of the brain and spinal cord at postmortem.

Charcot gained world-wide fame not because of these discoveries, but because of his interest in hysteria. In no small part, this was due to dramatic demonstrations of patients with hystero-epilepsy in meetings at the Salpêtrière, which were open to the general public.

At least initially, Charcot believed that hysteria was caused by an ‘organic’ lesion of the brain, which was beyond the reach of current techniques of investigation. This view was summarised by Zenner (1883): ‘Hysteria is a disease of the nervous system, perhaps affecting the entire nervous system; at least the great nervous centres are particularly involved. It depends upon peculiar pathological conditions of those centres which the microscope or other tests at present in our possession do not reveal. We therefore term it a functional disease.’ Charcot felt that there was a strong hereditary component, and noted that the signs could be induced or resolve under hypnosis. He also found that minor injuries had a role in provoking episodes. Unfortunately, events got out of hand.

On 23 and 24 August 1878, Professor Arthur Gamgee, Professor of Physiology in Manchester, accompanied by several physicians, visited the wards of the Salpêtrière, where Charcot personally demonstrated the signs of hystero-epilepsy. Gamgee published a detailed account in the *BMJ* of that year. Gamgee noted that hystero-epilepsy was ‘that remarkable disease almost all our knowledge of which is due to the labours of M. Charcot’.

The attacks of hystero-epilepsy typically had four phases; (1) the epileptiform stage; (2) phase des grands mouvements; (3) phase des attitudes passionelles; and (4) recovery.

The first stage was consistently provoked by ‘peripheral irritation’, such as ‘suddenly “gripping” the skin of the breast on both sides, about on a level with the fifth rib’. During the second stage: ‘The back being somewhat opisthotonically arched, the body was thrown with great violence and astounding rapidity alternately on to the occiput and heels.’ Gamgee described the following sequence of events in one patient during the third stage. First there was a posture of ‘clenched fists and menacing expression’, then ‘cowering, abject fear’, then ‘saintly happiness, as of one who realised the blessedness of heaven’. This was followed by ‘intense joy; the patient sees one whom she loves; she beckons to him to come, to come quickly; he has come ... Then succeed gestures which stamp this as the phase of lubricity’. Fear then returns and ‘fear takes possession of the patient; at first it is rats which she sees, and which she appears to fear the attack of ... it is obviously the fear of some human being which oppresses her, and causes her to beg for mercy’. The patient then hears strains of music; ‘she is pleased; she herself begins to hum the tune, but only for an instant’. Finally: ‘Her singing is followed by weeping, which is
broken by reproaches addressed to her parents as the cause of her misery.’ The fourth phase of ‘recovery’ could also be accompanied by hallucinations.

A characteristic feature of the attacks of hystero-epilepsy was that they could be stopped by pressure on an ovary: ‘At the instant pressure is made in the ovarian region, two results always follow: firstly, the patient’s mouth opens and the tongue is spasmodically extruded; and secondly the convulsions cease.’

There were other stigmata of hysteria including hyperaesthetic ovaries, anaesthesia and colour blindness (achromatopsia). There was a very distinctive form of hemi-anaesthesia and colour blindness as it could be transferred to the other side of the body by the use of magnets, solenoids, or metallic plates (phénomènon du transfert). Gamgee describes this in another patient. ‘There was complete anaesthesia on the right side, so that a needle could be thrust through the hand without occasioning the slightest evidence of pain.’ There was no sensory deficit on the left side of the body. A solenoid ‘was made to envelope the little finger of the right hemiaesthetic side. Almost instantaneously the sound side became hemiaesthetic and the previously normal eye became colour-blind for all colours but red whilst the powers of distinguishing colours on the usually colour-blind side became perfect. No sooner, however, was the finger withdrawn from the solenoid, than the anaesthesia and achromatopsia reassumed their usual distribution.’

Gamgee clearly believed that he was seeing an ‘organic’ problem. He was puzzled by the effects of magnets and solenoids ‘at a distance’ which were ‘absolutely inexplicable in the present condition of physiology’. He quoted Claude Bernard, who shortly before his death after witnessing one of Charcot’s demonstrations observed, ‘the facts show how little we do know’. Gamgee ended by making a plea for medicine and physiology to be more closely aligned.

Illustrations of the hystero-genic zones identified on the patient’s bodies by Charcot, and of the ‘ovarian compressor’ worn by patients for hours to ward off seizures, can be found in Shovron (2007).

Confirming that Gamgee was not somehow misinterpreting the situation, a series of lectures given by Charcot on the treatment of ‘grave hysteria’ with ‘metalloscopy’ and ‘metallo-therapy’ were published in *The Lancet* in 1878. Charcot described his treatment of hystero-epileptic attacks. ‘When I am called in under such circumstances the first thing I do is to practise compression of the ovary, and, to the utter astonishment of the parents, and perhaps also of the medical attendant, all the symptoms cease as if by magic. The young patient returns to consciousness with a look of surprise. But as soon as the compression is stopped the “fit” begins again. Consequently the treatment is not of any lasting value.’

Charcot went on to describe ‘metallo-therapy’ as a possible solution. Metals such as gold, copper, zinc and tin are in turn applied to an anaesthetic arm. With the correct metal there is a return of sensation sometimes within seconds, and usually within 15–20 minutes. At the same time, this previously weak arm develops ‘the strength of a man’. The transfer phenomenon may also occur. Once a metal is found to be effective, it could be dissolved in solution and given to the patient to drink. ‘We administer ten drops before each meal in a tumbler of distilled water.’

The memoirs of Jane Avril (Jeanne Beaudon), the dancer immortalised by Toulouse Lautrec, provide an insider’s account of life in the Salpêtrière at that time (Bonduelle and Gelfand 1999). Avril tells us: ‘I lived for two years in this “Eden” – which it was for me, so much in this world being relative … There were those deranged girls whose ailment named Hysteria consisted, above all, in simulation of it … How much trouble they used to go to in order to capture attention and gain stardom. That prize went to the one who would find something novel to overshadow the others when Charcot, followed by a large group of students, stood at the bedside and observed their wild contortions, “arcs de cercle”, various acrobatics, and other gymnastics. These patients had nothing to hide from little me – I was of so little consequence! – thus they didn’t hesitate to let me know about what they used to call “the secret”. They gave me the following directions: “when you see one of them come in, be sure to come to my bed and press hard on my ovaries”. It was understood that this simple manoeuvre would suffice to interrupt the attack immediately, permitting the “patient” – recovering her wits – to have a conversation with the special person of the moment. When they sensed that the time of Charcot’s visit was approaching, several threw a fit and I, now that the time had arrived, cooperated by doing what they had requested of me … ’

Avril concluded: ‘I was astonished every time to see how such eminent savants could be duped in that way, when I, as insignificant as I was, saw through the faces. I have said to myself since that the great Charcot was aware of what was happening …’ However, there were no confessions from the women with hystero-epilepsy. Baudouin in 1925 questioned Blanche Wittman, the ‘Queen of the Hysterics’, on her deathbed about what had happened: ‘if we fell asleep, if we had attacks, it was because we were helpless to do otherwise. What’s more, it was very unpleasant … Fakery! Do you think it would have been easy to fool M. Charcot? Yes, there were tricksters who tried; he used to glance at them and say: “Be still!”’ (Bonduelle and Gelfand 1999).

Charcot was aware of the possibility of deception (Goetz 2016). He also knew that outside the Salpêtrière, his actions were coming into question, but seemed untroubled by this. Pierre Marie wanted to denounce Dr JM Duncan, who at a meeting of the British Medical Association attended by Marie, had expressed doubts about ovarian compression stopping hysterical spells. Charcot advised not bothering about it. ‘Let him, therefore, stumble as he wishes; it is simpler and perhaps more appropriate. To start up a debate would involve, not a conversion, but a full education – lost cause. What does it matter to us?’ (Goetz 2003).

However, it seems clear that hystero-epilepsy in all its glory was an iatrogenic condition. It died with Charcot. For example, Clarke from Bristol writing in 1893, in a review of 70
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cases found that in contrast to the prevalence in the Salpêtrière: ‘I have not yet met with a case in which there were distinct hysterical stigmata, and conclude that such cases are rare.’ In 1909, Babinski, Charcot’s pupil, published a paper with the brutal title The Dismemberment of Traditional Hystera where he described Charcot’s views as ‘both insufficient and erroneous’. Babinski believed that the stigmata of hystero-epilepsy were produced by suggestion. ‘For some years I have not found the stigmata in hysterical patients not previously in contact with those capable of suggesting them.’ Babinski introduced a new word ‘pithiatism’, meaning induced by suggestion and cured by persuasion, which he felt should replace ‘hysteria’. He warned: ‘Realizing the extent of his influence upon suggestible patients, a doctor, while observing the sick person, should observe himself, and guard his words, remembering always that a question awkwardly put or an inopportune reflection may give a suggestion.’ Janet another pupil said of Charcot: ‘he described a type of hysterical which disappeared with him; nobody nowadays any longer describes the attack of hysteria as Charcot did’ (Janet 1920, p. 21). Wilson (1911) was less kind. ‘With the passing of the years the professional hystériques of the Salpêtrière, so assiduously cultivated by Charcot, have gone, or almost gone – or as Dubois reminds us, some, like old circus horses can still be found doing their turn.’

How Charcot accommodated an ‘organic’ concept of hysteria due to a functional lesion in the brain, with his practice of ovarian compression and the external and internal use of ‘metallo-therapy’ is not known. ‘Despite the fact that a great deal of literature has been devoted to Charcot’s work on hysteria, it must be said that he developed no general conception of the disorder that could be compared to Babinski’s. In the lessons devoted to hysteria, many of Charcot’s statements are repetitive or contradict each other. Moreover, the chronology of the lessons is not easy to establish, and Charcot’s thought is both complicated and evolved over time. Therefore different interpreters could emphasize different aspects of his work’ (Derouesne 2009). In 1892, the year before he died, in a preface to a monograph of Janet, Charcot wrote: ‘These works confirm a point of view that I have oftentimes expressed – which is that hysteria is for the most part a mental illness’ (Goetz 2016). However, there is little else published in his works that supports this position. Exactly what Charcot thought, and how the Salpêtrière itself became a hysterogenic zone, will probably never be entirely clear.

The story of Charcot and hysteria has been outlined in some detail because of the important lessons to be learned from it. The first is that when a ‘great’ gets it wrong, the results can be disastrous, as their opinions often go unchallenged. Charcot’s views were ‘expressed with authority and enunciated with dogmatism’ (Wilson 1911). Dogmatism has been a recurrent theme in the history of PNDs. A dominant figure and his followers insist that others show obedience to a particular theory. This is then passively accepted, with a loss of common sense, so that everyday patient experience that is at odds with the theory is ignored. The second lesson is that the Charcot’s ‘neurobiological’ approach so effective in delineating organic diseases, was not well suited to the challenges thrown out by hysteria. Janet’s view in 1920 was that Charcot did not sufficiently consider psychological causes. ‘Carried along by his habits as a clinician, he has, I think, sought these general laws too much in the physiological domain, which led him to a certain number of regrettable errors’ (p. 17).

It must also not be forgotten that, for many of the patients, the Salpêtrière was a place of refuge from a life of misery. The extreme hypnotisability, and the profound power of dissociation evident in the women of the Salpêtrière, suggest they may have been victims of severe sexual, physical and emotional abuse in their past lives. For them to be under Charcot’s care was as Jean Avril observed ‘this Eden’.

That by 1910, Charcot’s ‘functional’ meaning ‘organic’ theory had been replaced by the view that hysteria was mostly a psychological disorder, is clearly seen in an editorial published in the Lancet in May of that year. ‘The days of elaboration of comparisons and analogies between hysterical and organic phenomena, such as are associated with the school founded by Charcot, have been succeeded by a period when the interpretation of the disease is being sought in the realm of mind, when the symptoms of hysteria are being assigned to a disturbance of a psychological nature that maybe traced with precision through all hysterical manifestations. The revolt has been led by Babinski, Janet, and Freud, each of whom has played a noteworthy role in the dismemberment of the traditional hysteria.’

SIGMUND FREUD (1856–1939)

Charcot’s reputation has suffered because of his involvement in hysteria, but much of his work continues to be highly regarded, as it should. In contrast, in the last 20 or so years, Sigmund Freud, once routinely described as a genius has had an amazing fall from grace. His entire reputation has fallen into the ‘dark, unbottomed, infinite abyss’ of Milton. As an example, in 1967, in Collier’s Encyclopedia, Kardiner wrote: ‘The influence of Freud on contemporary civilization has been enormous. Though more recently it has been on the wane in Europe, psychoanalysis continues to be the dominant psychiatric method in the United States, and to a lesser degree in England … Psychoanalysis has thus in a way become the handmaiden of the society’s liberal-democratic assumptions and romantic belief in the possibility of almost limitless self-improvement … In the United States psychoanalysis has had a profound influence on literature and drama, most recently in the works of Eugene O’Neil and Tennessee Williams.’

Flem (1991) went further. ‘In two or three centuries, when psychoanalytic treatment will have long disappeared, there will be no doubt remain on the shelves of libraries, alongside the names of Shakespeare, Dante, Sophocles, Goethe, Proust, Borges, Peric and Celan, the name of Sigmund Freud.’ Contrast this with Tasker (1996) in an essay entitled ‘Burying Freud’: ‘The verdict has been uniformly negative: Freud as
a scientist, metapsychologist, and diagnostician of society emerges as a quack.’ Tasker continued: ‘The sheer crankiness of Freud’s ideas was concealed by his marvellous prose, which gave the ideas a veneer of clarity and a feeling of inevitability. Most cranks write badly. Moreover, his lunacy came from an unexpected angle: just like real science, analytical theory was difficult, technical, tough minded, and counterintuitive’.

Freud’s theory of psychoanalysis arose from his treatment of patients with hysteria, and there can be no doubt he made important observations. For example, in April 1896 Freud delivered a lecture, ‘The Aetiology of Hysteria’, before the Society for Psychiatry and Neurology, in Vienna (Masson 1984). In this Freud defined ‘the hysterical state’ as ‘a long persisting after effect of an emotion experienced in the past’. In trying to find the ‘traumatic scene’ that resulted in this state, he identified two requirements of the scene: ‘It possesses the relevant suitability to act as a determinant and it recognizably possesses the necessary traumatic force.’ Freud observed: ‘Here we meet with our first great disappointment.’ Although sometimes there is a clearly traumatic scene such as the sight of a decomposing dead body, ‘incomparably more frequently’ than finding a clear explanation the content of the scene bears no relation to the nature of the symptom, or the experience seems innocuous. Often it appears both unrelated to the symptom and innocuous. Further, ‘we also fail to secure any therapeutic gain’. In other words Freud observed that most people with hysteria did not have a clear psychological trigger for their problems, and treatment was often unsuccessful; very ‘modern’ observations.

Freud then unveiled to the audience his theory that sexual experiences in childhood were the cause of hysteria. These at times seemed ‘astonishingly trivial’. His lecture was not well received. In a letter to Fliess he describes the reaction of the audience: ‘an icy reception from the asses, and from Kraft-Ebbing, the strange comment: It sounds like a scientific fairy tale. And this after one has demonstrated to them a solution to a more than thousand-year-old problem, a “source of the Nile”’ (Masson 1984).

Ormerod (1914) described Freud’s subsequent revision of his theory: ‘At one stage of his investigations, on the basis of 13 cases, Freud stated that the events which started these ideas were actual criminal assaults on the patient in early life. This statement, as you may easily imagine, had to be given up; the stories of the assaults were simply phantasies of the patient, which both he and the psycho-analyst erroneously took to be true. The factors originating the hysteria had then to be sought still further back in life. From this necessity, it would seem, arose Freud’s theory of sexuality in the infant. ‘This theory is ingenious and interesting, but to my mind improbable and extremely disagreeable.’ In an accompanying editorial in the Lancet was the following observation: ‘if it is ridiculous that kills, it is a sense of humour that saves; and could some of the Freudian school show even traces of the latter they would not expose themselves so fatally to the former’.

The term ‘conversion disorder’ came from Freud but trying to understand exactly what Freud meant by it, seems difficult (Kanaan 2016). However, as a general concept it is extremely useful in discussing the diagnosis of a PND with the child and family. The simple idea that the child is under stress, but does not want to worry others, and tries to keep this out of her conscious mind, but it has to come out some way, and this happens in the form of physical symptoms, is something that many children and families find acceptable. It serves well in the crucial phase of breaking the news of the diagnosis.

It seems likely that Freud’s works will survive in some form, and it will be no surprise if at least some of his ideas come back into fashion in the not too distant future.

PIERRE MARIE FÉLIX JANET (1859–1947)

Following in the steps of his uncle Paul, Pierre Janet, initially trained in philosophy. He became interested in hysteria, and following completion of his medical studies, in 1893 he was appointed by Charcot to head a new experimental psychology laboratory at the Salpêtrière. (Charcot died unexpectedly weeks later.) We do not need to rely on a translation of Janet’s views on hysteria, as we mostly have to do with Briquet, Charcot and Freud. In 1906 Briquet gave 15 lectures on hysteria at the Harvard Medical School. These became the basis of a book written in English, The Major Symptoms of Hysteria, published in 1907, with a revised second edition in 1920. The citations discussed here are from the second edition. Janet’s ‘encyclopaedic scholarship, his meticulous and subtle clinical observations, his intellectual stature, and the originality of his theorizing’ (Gregory 1987) can all be found in this book. He was a man of strong views supported by extensive clinical experience.

In the first chapter Janet emphasises the importance of correct and early diagnosis. ‘This early diagnosis is much more important still from another point of view: it will keep you, allow me to tell you plainly, from making blunders. It is perhaps not very serious not to recognize a hysterical accident and not to treat it; but what is always very serious is to mistake a hysterical accident for another one, and to treat it for what it is not. You cannot imagine the medical blunders, and too often also the medical crimes, committed in this way’ (p. 11).

He describes the consequences. ‘Then the physician interposes, frightens the family, agitates the patient to the utmost, and prescribes extraordinary diets, perturbing the life and exhausting the strength of the sick person. Finally, the surgeon is called in. Do not try to count the number of arms cut off, of muscles of the neck incised for cricks, of bones broken for mere cramps, of bellies cut open for phantom tumours, and especially of women made barren for pretended ovarian tumours. Humanity ought indeed to do homage to Charcot for having prevented a greater depopulation’ (p. 12).

Illustrating that Janet’s message is not out of date, is the paper by Ferrara and Jankovic (2008), describing 54 children with psychogenic movement disorders. ‘Twelve (22%) children had a total of 17 surgeries for symptoms related to their psychogenic movement disorders (PMD) or for associated symptoms eventually determined to have no identifiable
organic basis. Procedures directly attributable to PMDs included: ulnar nerve transposition for arm stiffness and finger curling due to hemidystonia, shoulder stabilisation for painful arm posturing due to bifacial dystonia, three surgeries for painful thumb posturing due to bifacial dystonia, two arthroscopic knee explorations for pain associated with hemidystonia, bilateral ocular surgeries for misalignment due to convergence spasm, percutaneous endoscopic gastrostomy for dysphagia due to cranial dystonia … Edwards et al. (2011) described two patients who had limbs amputated for ‘fixed dystonia’ (discussed in The Syndrome of Fixed Dystonia section below) noting that: ‘The outcome of amputation in fixed dystonia is invariably unfavourable.’

Returning to Janet, in the chapter on hysterical paralysis he quotes Babinski and others: ‘According to these authors, this ensemble of signs is absolutely characteristic, and it is possible to recognize a hysterical hemiplegy solely through this objective examination which requires nothing of the patient’s psychological observation. The thing is perfect theoretically, but practically it is much more difficult than is supposed’ (p. 148).

When discussing hysterical sensory signs Janet notes that these ‘attend to the popular conception of the organ rather than to its anatomic conception’ (p. 157). He addresses the ‘apparently voluntary’ nature of hysterical symptoms: ‘The anesthésia of hystérical is extremely changeable and contradictory. These patients pretend not to feel, and by very simple artifices we can prove to them that they feel perfectly well. Their insensibility is, therefore, simulated, and our processes are only means to deceive a deceiver and unmask a fraud. This résumé of facts is, to our mind, altogether crude and insufficient. Do hystericals take any particular interest or pleasure in having their arms pierced through with needles? … How is it that, in all civilized countries, hystéricals should have agreed to simulate the same thing ever since the Middle Ages to the present day?’ (p. 171).

Janet was not convinced that hysterical problems were entirely of psychological origin, but accepted that for 20 years, the psychological conception has the mastery’ (p. 323).

Janet’s theories on hysteria were complex and philosophical. Key elements included a narrowing of the field of consciousness (analogous to a narrowing of the visual fields), and dissociation (Van Der Hart and Horst 1989). ‘Dissociation’ is from the French désagrégation, and means that functions such as moving, remembering or feeling, can be walled off into separate compartments, unable to be assessed by the conscious mind. ‘The function is far from being destroyed. It continues to exist and often even develops to an exaggerated degree. It is only suppressed from one very special standpoint; it is no longer at the disposal of the will or the consciousness of the subject’ (p. 319).

THE ECLIPSE OF HYSTERIA

From 1900 to 1965, speaking generally, ‘hysterical’ symptoms were ascribed to psychological problems. In the English-speaking world at least, this changed when Eliot Slater (1965) published a paper in the *BMJ* that had a profound effect on the way doctors viewed PND for the next 30 or more years. This paper is analysed in detail elsewhere (Morris and Grattan-Smith 2015), and will only be briefly discussed here. It was a follow-up study of patients seen at Queen Square in London, who had been diagnosed with hysteria. Slater ended the article with: ‘What, then, is our conclusion? Looking back over the long history of “hysteria” we see that the null hypothesis has never been disproved. No evidence has yet been offered that the patients diagnosed as suffering from “hysteria” are in medically significant terms anything more than a random selection … The only thing that “hysterical” patients can be shown to have in common is that they are all patients. The malady of the wandering womb began as a myth, and a myth it yet survives. But, like all unwarranted beliefs which still attract credence, it is dangerous. The diagnosis of “hysteria” is a disguise for ignorance and a fertile source of clinical error. It is in fact not only a delusion but also a snare.’ Slater took the view that the diagnosis of hysteria harmed patients, as it resulted in the underlying organic disease being missed, the opposite view to Janet who felt the diagnosis protected them from ‘medical crimes’, in particular, unnecessary surgery.

Slater’s claim was that when patients with ‘hysteria’ were followed-up, a large number were found to have organic disease. The details of exactly what had happened to these patients were difficult to retrieve from the paper. The rhetoric was brilliant, but the data on which it was based was not clearly presented. There was no analysis of where things went wrong, and to what extent the organic illness could have been diagnosed at the time of initial presentation. It was not clear whether the diagnosis of hysteria was made by neurology consultants, or by psychiatrists, or by junior staff. Nor was there a discussion of whether the symptoms on which the diagnosis of hysteria had been made, could be related to the subsequently identified organic illness.

Accompanying Slater’s paper, the *BMJ* published an editorial entitled ‘Eclipse of Hysteria’. The unnamed author, presumably a psychiatrist, completed the pincer movement. ‘Dr Eliot Slater … advocates that the diagnosis of hysteria should be completely abandoned … A follow-up study of cases diagnosed as hysteria in the National Hospital has confirmed him in his conclusion that a syndrome or disease entity “hysteria” does not exist. Dr Slater’s conclusions, striking and provocative though they are, will be acceptable to most psychiatrists.’

The defence of the diagnosis of hysteria fell to Sir Francis Walshe, whose paper was published in the *BMJ* in December 1965. Walshe was then 80 years old. There was little response from younger neurologists. Slater’s rhetoric was accepted without analysis of the details of his paper. For many years his claims became accepted fact. Although the effect was probably greater in adult neurology, paediatric neurologists who diagnosed hysteria were constantly warned that they were ‘missing something organic’. Large textbooks on paediatric neurology first published in the 1980s and 1990s such as those of Aicardi, Brett, and Swaiman and Wright, made only fleeting reference to hysteria.
The proposition that patients diagnosed with ‘hysteria’ were highly likely to have an underlying organic disease, which seemed to defy common clinical experience, went substantially unchallenged until 1998 when Crimlisk et al. published a paper entitled ‘Slater revisited: 6 year follow-up study of patients with medically unexplained motor symptoms’. This and multiple subsequent papers, including a huge study by Stone et al. (2009), have made it clear that an undetected organic disease is uncommon in patients diagnosed with PNDs. Accompanying this change in position has been a revival of interest in the study of PNDs, particularly from a neurobiological perspective, accompanied by attempts to find a more acceptable name, with a return to ‘functional’ the latest suggestion.

PAEDIATRIC PAPERS

Looking specifically at papers describing PNDs in children, between 1897 and 1907, four articles were published in the Journal of the American Medical Association with the identical title, ‘Hysteria in Children’ by Mayer, Burr, Biller and Hecht. Brief excerpts from these papers show that we face the same questions, and experience the same difficulties, as doctors did more than 100 years ago.

THE PREDICAMENT OF THE CHILD

Mayer (1899): ‘Often the cause of the child’s hysteria is fright caused by a drunken father nightly beating mother and child, or fear of a whipping by a stern teacher.’

Biller (1898): ‘[children with hysteria] suffer greatly from competitive examinations at school, and from the extra work that is often imposed upon them in preparing for school entertainments – especially in preparing for public recitations’.

THE PROVOCATION OF A PSYCHOCGENIC NEUROLOGICAL DISORDER BY MINOR INJURY OR ILLNESS

Hecht (1907): ‘That hysterical symptoms are frequently engrafted on symptoms of organic disease and long outlast the latter, is, of course, not to be lost sight of … Slight cause, then, and grave consequence should arouse immediately a suspicion of hysteria.’

CONTROVERSIES OVER THE CAUSE

Mayer (1899): ‘Before proceeding further let us see what the basis of hysteria is. It is a question often asked, but never answered. Still, there is an underlying groundwork to every case. We do not refer to hypotheses. Many of these have been advanced, as that of Janet, that hysteria is due to a weakening of the psychologic synthesis; of Myers, that it is due to a disease of the hypnoid stratum, and of Liebermeister that it is a subcortical disturbance.’

THE DIFFICULTY IN SEPARATING ORGANIC DISEASE FROM PSYCHOCGENIC NEUROLOGICAL DISORDERS

Hecht (1907): ‘The greatest difficulty lies not so much in mistaking organic disease for hysteria, and vice versa, as in failing to appreciate that organic disease may be and frequently is complicated by hysteria.’

MALINGERING

Mayer (1899): ‘Just as hard as it is to diagnose the hysterical or organic nature of an affection in some cases, is it to distinguish simulation from hysteria.’

TREATMENT OF THE SYMPTOM OR THE UNDERLYING CAUSE?

Burr (1897): ‘I have used the word cure several times. I wish it to be understood to refer only to the specific attack and not to the inherited predisposition. We usually cure not the hysteria but the attack … These children need not only treatment for the attack, but most careful education of the will and the emotions, to save them in the future from suffering from hysteria.’

TREATMENT DIFFICULTIES AND THE TENDENCY OF FAMILIES TO SEEK ALTERNATIVE METHODS

Biller (1898): ‘the patient becomes dissatisfied and passes, frequently, into the hands of some quack or charlatan, who thrives by accidentally – and probably unconsciously – knowing how to take advantage of some of the tricks of this powerful but susceptible enemy of the human family’.

PROGNOSIS

Hecht (1907): ‘Just a word in reference to the prognosis, which in children is infinitely better than adults.’

Relevant quotations from the greats of the past will continue to be included in the discussion that is to follow, because of their clarity, and as a reminder that PNDs may well be ‘as old as human nature itself’ (Wilson 1930).

FREQUENCY AND PRESENTATION OF PSYCHOCGENIC NEUROLOGICAL DISORDERS

David Taylor (1986) observed that hysteria ‘is a commonplace reaction, and those who become dignified by a formal diagnosis are a severe, extreme or fortuitous selection’. It is likely many children will have a brief episode that passes without either diagnosis or sequelae. Reflecting this, the study of Ani et al. (2013) was confined to children with ‘non-transient’ conversion disorder. Children who had a duration of illness less than 7 days, were excluded from their study.

There have been two recent surveillance reports of the incidence of conversion disorder (CD) in childhood. In the study
of Ani et al. (2013), over a 15-month surveillance period there were 204 confirmed cases in United Kingdom and Ireland, giving an estimated 12 month incidence of 1.30/100000. The age range of the 204 confirmed cases was 7–15 years, with a median age of 12.5 years. The incidence was 0.26/100000 among children younger than 10 years, and 3.04/100000 for children 10–15 years old. Three-quarters of the patients were females, and a female predominance was noted both in those older and younger than 10 years. There was no child younger than 7 years at the time of diagnosis.

In the study of Ani et al. (2013), core conversion symptoms included weakness (63%), abnormal movements (43%), non-epileptic seizures (40%), anaesthesia/paraesthesia (32%), diminished consciousness (29%), visual loss (23%), limb paralysis (22%), loss of speech (19%) and hearing loss (8%). Most children (69%), presented with more than one core symptom, and 16% had four or more symptoms. Pain (8%). Most children (69%), presented with more than one core symptom, and 16% had four or more symptoms. Pain (56%) and fatigue (34%) were commonly reported alongside the core symptoms, with la belle indifference found in 27% of children.

In the earlier surveillance study of Kozlowska et al. (2007), of 194 Australian children under 16 years of age, the annual incidence of conversion disorder was 2.3/100000. In children younger than 10 years of age, the incidence was 0.8/100000. In the state of New South Wales the overall incidence was 4.2/100000 perhaps due to more diligent reporting. Seventy-one per cent of the children were female. The average age at presentation was 11.8 years, and 55% had multiple conversion symptoms. The most common presentations were disturbance of voluntary motor function (64%), including motor weakness, limb paralysis, abnormal gait, abnormal movements and difficulties with speech or swallowing. Sensory symptoms (24%), pseudoseizures (23%), and respiratory problems (14%) were also found. As well as the conversion symptoms, pain (56%) and fatigue (34%) were commonly reported.

Surveillance studies can only paint a broad picture, but a number of earlier case based series described similar results to those found in these two surveys (Schneider and Rice 1979; Grattan-Smith et al. 1988; Leslie 1988). In the review of Grattan-Smith et al. (1988), the records of 52 children admitted to hospital with conversion disorder over a 10-year period were reviewed. The findings were almost identical to the surveys of Ani et al. (2013) and Kozlowska et al. (2007). Seventy-five per cent of the children were female and 62% were between the age of 10 and 12 years. There were only three children under the age of 8 years. An abnormal gait was present in 66%. Of those with an abnormal gait, 44% could not move at all with leg pain, and most of the remainder had classic presentations such as monoparesis, paraplegia, hemiparesis and ataxia. Other presentations included non-epileptic seizures, sneezing, stridor, aphasia, and globus hystericus. Overall, 77% of the patients complained of pain, paraesthesia, or anaesthesia. This co-existence of motor dysfunction and sensory disturbance in patients with PNDs has long been recognised. Briquet observed: ‘Pain in the muscles is so common that there is not a single woman with this neurosis who does not have some muscle pain during the course of the illness’ (Mai and Merskey 1980). Janet found anaesthesia was a feature of two-thirds of hysterical presentations (Janet 1920, p. 276).

From multiple sources, a consistent picture emerges of the presentation of a child with a PND. The child is most often between 10 and 14 years of age, is female, has multiple symptoms and, as well as loss of function, frequently also complains of pain, sensory disturbance and fatigue. The condition is uncommon under the age of 8 years.

The ‘Positive Signs’ of a Psychogenic Neurological Disorder

The diagnosis of a PND is primarily based on the physical signs which reveal that, although the child complains of not being able to move, or feel, or see normally, these functions are intact. Normal investigations and the child being in a stressful situation add further weight to the diagnosis, but they are nothing without the signs.

In 1922 Henry Head described the ‘positive signs’ of hysteria. ‘These physical signs are as definite and specific as those of any other disease. Hysteria is sometimes said to “imitate” organic affections; but this is a highly misleading statement. The mimicry can only deceive an observer ignorant of the signs of hysteria or content with perfunctory examination.’ Subsequent authors adopted a more cautious approach and described ‘red flags’ that alert the examiner to the possibility of a PND. In their review of psychogenic movement disorders in adults, Gupta and Lang (2009) list ten clues obtained from the history, and 16 found in the examination that suggest the diagnosis, warning that ‘no single clinical finding is pathognomonic’. More recently it has again been claimed that, in experienced hands, certain signs are diagnostic of a functional movement disorder (Espay and Lang 2015).

In this section the various signs that are seen in PND are reviewed. Most of these have been recognised for more than 100 years (see Clarke 1893). More detailed accounts can be found in the older textbooks such as Walsh (1952), and De Jong (Haerer 1992) and the monograph by Weintraub (1977). There has also been a more recent review of the signs of conversion disorder (Daum et al. 2014), and a video-based ‘Manual’ demonstrating some of the signs (Morris and Grattan-Smith 2015). Most recent is the comprehensive review of all aspects of PND found in an edition of The Handbook of Clinical Neurology devoted to PND (Hallet et al. 2016).

Abnormalities of Gait

Abnormalities of gait are particularly common in children with psychogenic disorders. When the child cannot walk normally,
the message that help is needed is inescapable. Mayer (1899) provides a beautiful description of the psychogenic gait: 'The gait resulting from functional paralysis of the lower limbs is peculiar. It is jerky, not halting nor hesitating, the steps taken being small and noticeably forced. There is no spreading of the legs, as in organic incoordination, no high-step with foot-drop, as in infantile paralysis and multiple neuritis, no scythe-like motion as in organic hemiplegia with the turned-in toes catching on the floor at each forward step. The muscles impress you as being unnecessarily used rather than being useless.'

Clarke (1893) described a dramatic case in a 12-year-old boy. 'On Feb. 9th, 1892, he was carried to the hospital as he could not walk. When placed on his feet he did not fall, but could not stand still, constantly shifting his feet. He could not walk, run or stand still, but on being placed on his feet went round and put in a chair. He moved with a curious, quick, dancing step, in which the feet were brought rather forcibly to the floor. The movement is difficult to describe, but one of the nurses said the step was known in country dances as the ‘monkey hornpipe’. Whether the eyes were closed or open seemed to make no difference to him. There were no other signs of nervous disease. The next day he was still entirely unable to walk or run, but could get along very well by jumping with his feet close together or by going on all fours, and was able to hop down the ward and back. In a few days he recovered the power of walking and running.' Such dramatic presentations continue to be seen.

In the so-called ‘magnetic’ gait, the feet may seem stuck to the ground and the steps are short, slow and done with considerable effort. At the same time the child may groan and gives the impression of a diffusely painful body. Dubowitz and Hersov (1976) noted a variant of this: ‘Three of the cases also demonstrated what we have come to regard as a very useful sign of hysterical paralysis, namely an inability to raise the foot off the floor when attempting to stand or hop on one leg (almost as if the foot were glued to the floor). The effort is always associated with exaggerated movements and contortions of the other limbs.’

At the other extreme is a staggering gait with the child lurching from side to side, and continually threatening to fall, but actually displaying superb balance in the ability to, without mishap, continually move from one precarious posture to another. This is often called ‘astasia-abasia’.

The fact that a gait is bizarre does not make it psychogenic. Dystonic gaits may look very strange, and patients with DYTI dystonia may be forced into severe twisting postures without falling. Chorea can also produce a bizarre gait that is often mistaken as being psychogenic.

Once the question of a psychogenic gait has arisen, the child needs to be examined carefully in bed. The absence of any abnormalities of tone, the finding of normal reflexes, and a negative Babinski sign are all helpful. However, often it is the presence of additional psychogenic signs, such as non-dermatomal sensory loss or monocular double vision, that is decisive in making the diagnosis of a PND. Sometimes the child will be seen to walk normally when, for example, going to the toilet and unaware of being observed. In very difficult cases it may only be the return of a normal gait with treatment that finally sets the clinician’s mind at rest that the problem is definitely a PND.

**PSYCHOGENIC WEAKNESS**

Testing of psychogenic weakness can be difficult, as at times it relies on the subjective impressions of the examiner. As an example from Walshe (1952): ‘The hand grasp of a partially paralysed arm in the case of hysterical weakness has characteristic features: the hand is closed round the observer’s and held firmly set in a grasp which exerts but the slightest pressure and the sense of power withheld is one that once felt is not easily forgotten.’ From Head (1922): ‘Sometimes movement is positively inhibited; the patient says, “I cannot move my leg”, and it hangs inert, or is dragged behind him like a log.’

A sign probably first described by Beevor has had a number of different names including ‘defective inhibition of the antagonists’ (Wilson 1930). Walshe (1952) called it the ‘law of antagonistic effort’ – ‘if the request be made to the patient to flex the forearm strongly on the arm against resistance, a distinct movement of extension may be felt’. It is also described in Head’s paper. ‘On each occasion he responded to your command by an exactly opposite movement’ (Head 1922). Wilson (1930) regarded this initial activation of antagonist muscles as ‘unquestionably the most common motor sign’ of hysteria.

In 1908 Hoover made an observation that has become the basis of a useful test for detecting psychogenic weakness of one leg. ‘If a normal person, lying on a couch in the dorsal position, be asked to lift the right foot off the couch with the leg extended, the left heel will be observed to dig into the couch as the right leg and thigh are elevated.’ The Hoover test can be performed in a number of ways, and the following is one method. The child lies supine and is asked to lift the ‘good’ leg from the bed and resist the examiner, who exerts downward pressure on that leg with one hand. The examiner’s other hand is placed under the ankle of the ‘weak’ leg. As the child pushes upwards against the examiners hand with the good leg, strong downward pressure is felt in the ‘weak’ leg with the other hand. The examiner then tests the ‘weak’ leg. There is difficulty lifting it from the bed. The examiner then lifts the weak leg up from the bed with a hand under the ankle. The child is asked to push the hand into the bed. There is either minimal, or no downward pressure at all, in the ‘weak’ leg, whereas seconds before it pushed the hand strongly into the bed. This clearly demonstrates the child is not as weak as claimed.

Other inconsistencies may be noted. The child may be unable to move the foot in any direction while in bed, but when standing, can walk on the toes without difficulty. A boy apparently paralysed and in a wheelchair, may suddenly kick a ball across the room. There are many such examples, with the underlying principle showing that the child is not weak as claimed.
If it can be demonstrated that not only does the patient have normal strength when claiming to be weak, but reacts to this demonstration by some form of counter move, then the diagnosis of a PND is even more secure. Head (1922) gives an example: 'In the milder examples of loss of power or inability to stand on one leg, the nature of the affection is revealed by the following trick. If it has been determined to the satisfaction of the patient that he cannot support his weight on the right foot, tell him you are quite satisfied that the right is affected, but that the left is his "good leg". When he is standing steadily, give a sudden command, "Kick out your good leg"; this he will do, although it necessitates balancing himself upon the affected foot. On the other hand, follow this quickly with the order, "Kick out your bad leg", and he will fall, although he is supported on the normal limb.'

These tests are important in making the correct diagnosis, but at the same time it is important to avoid making the child feel like a ‘fraud’, which can easily cause both an escalation and an entrenchment of the symptoms. If, in front of his parents, you suddenly lob a soft toy at a boy who plays cricket, and before he knows it his ‘paralysed’ arms springs out and catches the toy, from that moment on you are unlikely to have much of a relationship with the boy. (If he does not react and the toy lands on his chest, and he cries out in pain and shock, things will be even worse.)

Potentially painful tests should also be avoided. For example, a test used for unilateral arm weakness in adults is to lift the weak arm above the patients head, and let it drop. In psychogenic weakness rather than falling straight down towards the face, the arm tends to veer away and land on the bed next to the patient. Psychogenic coma is not discussed in this section, but if this is suspected, jiggling a rolled up tissue back and forth in a nostril is irritating, but harmless, and is to be preferred to methods such as strong supra-orbital pressure, or squeezing the nipples. An example of a painful test from the past used on adults is the test for hysterical paraplegia attributed to Gowers (Pryse-Phillips 1995). It consists of suddenly pulling on the pubic hair of the patient with paralysed legs, causing the legs to immediately adduct. Such painful tests may be a reflection of the level of anxiety in the doctor, rather than a desire to punish the patient. However, they are a high-stakes game as the patient may pass the test, ‘proving’ that they do not have a psychogenic problem. An example can be found in the movie Dirty Rotten Scoundrels where the ‘celebrated Liechtenstein psychiatrist’, Dr Emil Shaffhausen (Michael Caine), mercilessly whips the allegedly anesthetic legs of Freddy Benson (Steve Martin) who manages to stay silent throughout the ordeal.

LATERALISATION OF SIGNS

A common belief in adult patients with PND, perhaps going back to Briquet, was that when the signs were lateralised, this was more likely to be to the left. However, Stone et al. (2002) reviewed 121 studies, involving 1139 patients, and found that this was probably incorrect. Regan and LaBarbera (1984), found that ten of 11 children and adolescents with unilateral conversion symptoms, showed symptoms on the right side of the body. All were right handed. The only person with left-sided signs was a girl who developed pain in her left knee, and she had experienced an injury to that knee in the past. Schwingenschuh et al. (2008) found that when an abnormal movement started in one limb, it was the dominant side in nine of ten cases. In many studies, lateralisation is not discussed, and although these findings are interesting, it would be unwise to suggest that a problem is or is not psychogenic, based only on whether or not the dominant side was involved.

POSITIVE BABINSKI SIGN AND ANKLE CLONUS

It might be assumed that a positive Babinski sign, or what appears to be sustained ankle clonus, would be clear indications of an organic disorder. However, interpretation of the Babinski sign is difficult, and if the toe appears to be upgoing without any other signs of an upper motor neuron lesion, it should be viewed with caution. Psychogenic clonus can be very impressive, but has long been recognised as a clinical entity (Wilson 1930; Hallet 2010). Obviously great caution is required and the clinical setting is important. The author vividly remembers as a registrar being involved in the treatment of a teenage girl who had psychogenic seizures lasting 30 minutes or more. When examined she had very brisk reflexes and sustained ankle clonus. Both diagnosis and management were extremely difficult. The admission lasted months, and although while in hospital the girl vehemently denied any possibility of her having psychological problems, she later wrote to the consultant saying that she had been abused, and why did it take so long to make the diagnosis?

PSYCHOGENIC CHOREA AND DYSTONIA

The more common error in the setting of chorea and dystonia is to wrongly assume that the child has a psychogenic disorder. The emotional lability, the restlessness, the facial grimacing, the motor impersistence, and the dancing quality of the movements, can all lead to chorea being misdiagnosed as a psychogenic problem. Sydenham recognised this more than three centuries ago: ‘At first it shows itself by a halting, or rather an unsteady movement of one of the legs, which the patient drags. Then it is seen in the hand of the same side. The patient cannot keep it a moment in its place, whether he lay it upon his breast or any other part of his body. Do what he may, it will be jerked elsewhere convulsively. If any vessel filled with drink be put into his hand, before it reaches his mouth he will exhibit a thousand gesticulations like a mountebank. He holds the cup out straight, as if to move it to his mouth, but has his hand carried elsewhere by sudden jerks. Then, perhaps, he contrives to bring it to his mouth. If so, he will drink the liquid
Ross described two young women, aged 22 and 20 years who were suffering with this very difficult condition. In 1956 Macalpine and Ross cited Charcot who in 1890 had observed that this disorder is characterised by ‘non-pitting oedema, coldness, purplish discoloration, altered sensation, often total anaesthesia, paresis, and contracture of either hand or foot’. Pain was sometimes, but not always, a feature. Gold (1965) subsequently described six children with the same condition but used the term ‘hysterical contractures’.

**PSYCHOGENIC TREMOR**

When movements are repetitive and rhythmic, the child is usually described as having a tremor. In psychogenic tremor the movements may be of high amplitude and violent. When the patient is distracted, there may be a pause, or a change in frequency, amplitude or distribution. There can also be an alternating tremor where one arm rises as the other falls. Complex movements that resemble arm waving, patting or stroking can also be seen.

Distraction and entrainment are commonly used in the diagnosis of a psychogenic tremor. An example of distraction is as follows. The patient is asked to hold her arms out in front, and then do ‘serial 7s’ (taking 7 from 100, and then 7 from that number, and continuing downwards). With an organic tremor, the movements tend to worsen, whereas with psychogenic tremor they may disappear entirely. It is important to ensure the mental task is challenging. For example, asking an adolescent to count backwards from 10, or say the days of the week backwards, may not require sufficient mental effort, defeating the purpose of the task. If the child, who otherwise seems cognitively intact, gives answers that are hopelessly wrong, the test is not reliable, except in the sense that it raises the possibility that the problem is psychogenic.

Entrainment is used when the patient, for example, has a tremor of the right arm. The examiner sitting opposite the patient begins to tap against his leg with his right hand, and asks the patient to follow this exactly with her left hand. The examiner then taps on his leg varying the frequency, rhythm and amplitude. As the patient follows with her left arm, the tremor in her right hand changes, and in a classic situation takes on the identical rate and rhythm of the examiner. More often there is a perceptible change in what previously had been a consistent movement. If the patient inexplicably does not make a reasonable effort to follow the examiner’s movements, the test is not useful, apart from again fostering the suspicion that the problem may be psychogenic.

Certain patterns of tremor also raise the possibility of a psychogenic cause. A resting tremor is rare in children except for infants with inborn errors of dopamine metabolism (Grattan-Smith et al. 2002). A tremor that is present at rest, with posture and with action is also rare in childhood. (The exception is Holmes tremor, but here there has usually been a clear preceding cause such as severe head trauma.)

**THE SYNDROME OF FIXED DYSTONIA**

**Causalgia-Dystonia, Post-traumatic Dystonia**

There has been considerable controversy over the nature of this syndrome (Bhatia et al. 1993; Schrag et al. 2004). Typically after minor trauma, a limb develops a fixed immobile posture often associated with severe pain. Common postures include sustained foot inversion with plantar flexion, and wrist and finger flexion. There is overlap with Chronic Regional Pain Syndrome Type 1 (van Rijn et al. 2007). There is no space to cover the controversy about this condition in any detail but Hawley and Weiner (2011) have made their views clear: ‘Evidence supporting a pathophysiologic mechanism for peripheral trauma inducing or provoking dystonia is virtually non-existent … The literature clearly supports the view that fixed dystonia is a psychogenic movement disorder.’

Once again a knowledge of medical history is useful in dealing with this very difficult condition. In 1956 Macalpine and Ross described two young woman, aged 22 and 20 years who had been referred for sympathectomy or amputation because of the severity of their symptoms. The authors used Charcot’s term *œdème bleu des hysteriques* and noted that both Brodie (1837) and Paget (1873) had described the same condition. Macalpine and Ross cited Charcot who in 1890 had observed that this disorder is characterised by ‘non-pitting oedema, coldness, purplish discoloration, altered sensation, often total anaesthesia, paresis, and contracture of either hand or foot’. Pain was sometimes, but not always, a feature. Gold (1965) subsequently described six children with the same condition but used the term ‘hysterical contractures’.

**Off at a gulp; as if he were trying to amuse the spectators by his antics’** (Park and Park 1990).

Dystonia also has many features that may suggest to the unwary that the problem is psychogenic. At rest, tone may be normal, but it rapidly increases when movement is attempted. Dystonic patients may have gait abnormalities bizarre and, where despite the adoption of extreme postures, they do not fall. The ability to walk backwards better than being able to walk forward, is a commonly cited feature of a dystonic gait. More useful in practice is the observation that when walking, the arms of a patient with dystonia may twist up behind them. In the author’s experience this is uncommon with a psychogenic gait.

Dystonic jerking movements of the arms may also appear bizarre, for example, preventing the patient from being able to touch his nose on command. Suggestion can improve dystonic symptoms, and stress may worsen them. Dystonia can switch sides, improving on one side as the other worsens. ‘Gestes’ and task specific dystonias are not commonly identified in children (see Chapter 19). As a result, when a ‘geste’ is present, it is likely to be regarded as psychogenic by those who have not seen this characteristic sign of dystonia before. A rapid onset of symptoms is commonly cited as suggestive of a psychogenic problem, but this is also a feature of rapid onset dystonia parkinsonism (Brashear et al. 2007). Particularly difficult is the problem, but this is also a feature of rapid onset dystonia parkinsonism (Brashear et al. 2007). Particularly difficult is the situation where the patient carries a known dystonia causing gene, and possibly has a PND (Bentivoglio et al. 2002).

With the advent of the internet it is likely that psychogenic chorea or dystonia will be more commonly seen than in the past. [Avila and Cohen (2010) discuss the story of Desiree Jennings, a cheerleader, who provoked considerable online controversy as to whether she had organic or a psychogenic dystonia.]

If there is doubt about the diagnosis of psychogenic chorea or dystonia, it is prudent to get an opinion from an experienced and sensible colleague.
Tremor studies can be helpful. Canavese et al. (2008) found that with psychogenic tremor, polymyography showed a tremor activity with variable frequency and amplitude, which tended to decrease with distracting manoeuvres. It can be argued that this simply reflects the clinical findings. However, such studies can be very helpful in persuading the child and family that the problem is being carefully considered, and that sophisticated testing is being done to make sure the problem is not organic. To their minds it provides ‘scientific’ proof of the diagnosis, rather than it just being the opinion of a doctor.

Edwards and Bhatia (2012a) believe that the key clinical feature that helps to differentiate psychogenic tremor from organic tremor is that psychogenic tremor changes when attention is directed towards the affected limb. However, looking at the clinical features and neurophysiology (in adults) they concluded: ‘We found that no single measure had sufficient specificity and sensitivity to differentiate FT (functional tremor) from organic tremor.’

In the differential diagnosis of a psychogenic tremor, it is important to consider Wilson’s disease (which can present as a ‘psychiatric’ problem), and thyrotoxicosis (see Chapter 19).

**PSYCHOGENIC PALATAL TREMOR**

**Palatal Myoclonus**

Palatal tremor is a distinctive condition, and rare in childhood. Classically, palatal tremor is subdivided into symptomatic and essential palatal tremor (Deuschl et al. 1994). Symptomatic palatal tremor results from lesions involving the dentate-olivary pathway, and there may be hypertrophy of the inferior olivary nucleus, which can be demonstrated on magnetic resonance imaging (MRI) scans. The palatal movement is produced by contraction of levator veli palatini. There may be widespread jerks involving muscles of many areas including the face and diaphragm, which are synchronous with the palatal movements. There are no ear clicks. In essential palatal tremor, the movements result from contraction of tensor veli palatini. Ear clicks are commonly present, and the movements are restricted to the palate. There are no abnormalities of the inferior olivary nucleus on MRI.

In some patients with essential palatal tremor the problem appears to be psychogenic (Stamelou et al. 2012). The diagnosis is made on similar grounds to psychogenic tremor in other parts of the body, that is, changes with distraction. There is a dictum going back at least to Paget (1873) and Möbius (Hecht 1907), that if the examinee is unable to perform an unusual movement, then it is unlikely to be psychogenic. This is not reliable and psychogenic palatal tremor is an example.

**PSYCHOGENIC JERKS**

With psychogenic jerks, the movements are abrupt and short-lived. They may be difficult to distinguish from myoclonus, or an exaggerated startle response. A sense of generally exaggerated reactions is a clue to a psychogenic cause. A slight noise may cause the whole body to jerk. The knee jerk is tested and both arms and legs jerk. At the same time the patient complains that the light tap caused extreme pain over the patellar tendon.

In psychogenic myoclonus, especially if the jerks are not frequent, diagnosis can be very difficult. Neurophysiology can be helpful. A normal myoclonus makes typical epileptic myoclonus unlikely, but movement at the time of the jerk can obscure the recording. If, on surface electromyography (EMG), bursts are less than 50 ms then the person is likely to have a form of cortical myoclonus and the problem is not psychogenic (see Chapter 19 for a review of neurophysiology of myoclonus). Longer EMG bursts can occur in both organic movement disorders, and PND. The presence of giant somatosensory evoked potentials points to a cortical myoclonus, as does back averaging (Edwards and Bhatia 2012a), but this requires a sophisticated laboratory and a co-operative child.

Hyperekplexia needs to be considered in the differential of a psychogenic startle response, but usually the jerks have been life-long rather than of recent onset. With psychogenic startle, on neurophysiology testing the latency of the response and its EMG signature conform to that of a voluntary movement, rather than a true reflex response (Pal 2011). To a degree, this lag between the stimulus and the response can be identified clinically. The onset of stiff-man syndrome can be in childhood (Clardy et al. 2013), with emotional stress and anxiety provoking painful limb and paraspinal muscle spasms, and an exaggerated startle. Startle seizures also need to be considered (Aguglia et al. 1984).

**PSYCHOGENIC TICS**

Psychogenic tics were described many years ago (Dooley et al. 1994), but have received less attention than other PND. The diagnosis is particularly difficult as both tics and psychogenic movements can wax and wane, are made worse by stress, decrease when the person is distracted, and can look both voluntary and bizarre. In children with Tourette syndrome, typically tics start around the age of 5 years, and most often the initial tics are simple, such as shoulder shrugs or sniffing. Over time more complex tics develop. If a child of 13 years, who has never previously had tics, suddenly develops a complex movement that could be a tic, a psychogenic problem should be considered, realising that it could still be a tic.

In children with established Tourette syndrome, the diagnosis of psychogenic tics is especially difficult, and often can only be suspected. For example, the child develops deafening shrieks done at a time when they will have maximum impact. Is this a new vocal tic, an elaboration of a tic, or entirely psychogenic? Unless the child tells you it is not a tic, the differentiation is almost impossible. There can also be episodes labelled ‘tic attacks’, where there are sudden bouts of extremely severe tics often induced by anxiety (Robinson and Hedderly 2016). These may last hours with the child rushed into the nearest Accident and Emergency department, because of the
severity of the movements. In this setting the same questions is asked as to whether the movements are all tics, or is there an additional psychogenic component?

A point of differentiation with motor tics and psychogenic movements is functional loss. For example, a child with blinking tics will not close his eyes at the instant a cricket ball is being bowled to him. Tics tend to slip in between important actions, rather than disrupting them. If the movements cause the child to drop his pen, or gouge a hole in the paper he is writing on, the cause is unlikely to be a tic, and could be psychogenic (or another movement disorder).

Baizabal-Carvallo and Jankovic (2014) described nine adults with psychogenic tics. All had other psychogenic movement disorders at the same time or during the follow-up evaluations, which is an obvious clue. Other features included a lack of a premonitory sensation, and an inability to transiently suppress the movements. Unfortunately these features are less helpful in children. Children with Tourette syndrome often report that the movements just happen without warning, and that they have no control of them. Dooley et al. (1994) felt a differentiating factor was that the psychogenic tics were not stereotyped from one instance to the next. Ahmed et al. (2008) noted that with psychogenic tics the movements disappeared completely when the patients thought they were not being observed, and reappeared suddenly when they were re-examined. This is suggestive of a psychogenic cause, but certainly can occur in children with tics.

**PSYCHOGENIC DISORDERS AFFECTING THE EYES**

Psychogenic disorders affecting the eyes may occur in isolation, or in the company of multiple other psychogenic problems. Sometimes they are ‘discovered’ during an examination. A close co-operation with an ophthalmologist is usually very important in the diagnosis, as the ophthalmologist has multiple tools to unequivocally demonstrate that visual function is normal, despite complaints of visual impairment. There have been a number of excellent reviews of these techniques (Chen et al. 2007; Bruce and Newman 2010).

Observing the patient can be helpful. The child may complain of severe loss of vision, and yet be able to walk around obstacles without difficulty. He or she may complain of being unable to see what the teacher is writing on the board, or be unable to read schoolbooks, but can watch television from a considerable distance in the waiting room, and retain the ability to send and receive text messages on a mobile phone. In adults, the wearing of dark sunglasses into the examination room may suggest the possibility of a psychogenic disorder (Bengtzen et al. 2008).

With monocular visual loss, it is important to look for an afferent pupillary defect (Marcus Gunn pupil). In unilateral retrobulbar neuritis with visual loss, the disc may be normal, but an afferent pupillary defect will be present. If the patient complains of profound unilateral visual loss and there is no afferent pupillary defect then the problem is likely to be psychogenic (Bruce and Newman 2010). Obviously this is dependent on the examiner’s familiarity with the test.

Methods which allow the ophthalmologist to demonstrate normal vision when the complaint is monocular visual loss, include testing stereopsis, coloured lenses, polarised lenses and ‘fogging’ lenses (Chen et al. 2007; Bruce and Newman 2010). These tests can prove that the ‘bad’ eye has vision, and also document the amount of vision present.

Bilateral psychogenic visual loss is a more difficult problem. With psychogenic partial visual loss, the visual acuity does not improve when the distance from the eye chart is halved. Plane lenses can be given with the suggestion that they will improve visual acuity. With psychogenic total visual loss, the patient may be unable to localise the examiner’s voice when asked to do so. Further, they may not even be able to point to the location of their own hands, or touch the tip of one index finger against the other, findings that cannot be explained by poor vision. Suddenly threatening to poke them in the eyes may cause them to jump backwards, but as discussed above, this is not advised as it has an element of exposing the patient as a ‘fraud’. Moving a mirror in front of their face, or inducing optokinetic nystagmus, are ways of demonstrating that an apparently blind person can see.

Great care must be taken when there is an acute or subacute bilateral loss of vision. Problems such as sudden bilateral occipital infarction are rare in children, but there are a large number of potential causes of this symptom. Conditions such as Leber hereditary optic neuropathy, and retinal degenerations also have to be considered. In younger children with neuronal ceroid-lipofuscinosis visual deterioration associated with behaviour change can lead to a misdiagnosis of a psychogenic problem (Collins et al. 2006). Misdiagnosing an ‘organic’ problem as psychogenic is an abiding fear for most doctors. When the problem is visual loss the stakes are even higher than usual, as the organic disorder often has a catastrophic prognosis.

The commonest psychogenic visual field defect is ‘tunnel vision’ or tubular eye fields. Here there is bilateral loss of peripheral vision. The visual fields are circular without the usual temporal widening, the fields remain the same size no matter how far from the patient they are checked, and there is a sharp border. Sometimes jagged or spiral fields are found.

Double vision is a common psychogenic symptom, and may be easy to diagnose in the younger child. For example it may be present on looking straight ahead, and as a pen is brought towards the nose, the child may see an increasing number of pens – ‘two, four, six, lots’. Monocular double vision is a clue to a psychogenic disorder, but this is also rarely found with retinal disease, refractive errors, and abnormalities of the cornea and lens. It is one of many situations where an expert ophthalmological examination may be necessary before the diagnosis can be made.

An evolving abducens nerve palsy may produce double vision before obvious failure of abduction of the eye is noted. As another anecdote, the author remembers a girl in her early
adolescence who presented to the Accident and Emergency department and was thought to have ‘functional’ diplopia. She complained of double vision only when looking to the right. She was accompanied by her mother, a Shakespearian actor, and her father who wore an eye patch due to an earlier injury. A partial right lateral rectus palsy was noted. This was the first sign of her Guillain–Barré syndrome, and the following day she had to be ventilated because of a rapid progression of weakness with respiratory failure.

‘Convergence spasm’ is a psychogenic problem that can resemble either unilateral or bilateral sixth nerve palsies. The characteristic feature is that when the child is asked to look to one side, that eye does not move laterally but the pupils constrict. This is another example of the ‘signs’ of a PND being signs of normal function. The accommodation reflex is part of normal physiology, and occurs when looking at an object close to the nose. The eyes converge, the ciliary muscle contracts to increase the convexity of the lens, and the pupils constrict to increase the depth of focus. This reflex is activated in convergence spasm.

Disturbance of colour vision was common among the hysteric’s of the Salpêtrière (Gamgee 1878). It still occurs and usually the diagnosis is not difficult. Tiffany’s (1907) account of a 9-year-old girl remains relevant today. ‘She came from school and said that during the afternoon, while studying, the page suddenly became red. ‘Thereafter she complained of all colors appearing red, with the exception of objects of red color, which looked white ... While in my office the father designated several articles of red color and she would instantly call them white, or he would point to some white object and she would say it was red’. Testing with coloured lenses showed, what under other circumstances, would have been regarded as ‘malingering’. The girl had a slight convergent strabismus and it was suggested that an operation might be needed to cure the colour blindness. ‘The next day’ at 5 o’clock’ the problem ‘disappeared as suddenly as it came’. Tiffany made the same puzzled observation that many have made. ‘If this phenomenon had occurred in a willful, intractable, disobedient child, one would not have been so baffled for a cause of the malingering, but M. is a modest, obedient, rather retiring little girl of an excellent family.’

Many apparently typically developing children complain of transient large coloured blobs in their visual fields that can move around, or objects that temporarily appear too large or too small. There is no associated headache, and no signs, and the symptoms do not interfere with sport, or their use of computer games or social media. Investigations such as MRI of the brain and EEG are normal. The parents can be reassured that this is a common complaint, which seems benign with usually no cause found, and there is no need to pay attention to the symptoms. Stress can be mentioned as a possible contributory factor, but if there is little else to support this possibility, it does not seem sensible to overly emphasise this.

In patients with visual snow there is a disturbance of the entire visual field which resembles the ‘static’ or ‘snow’ of a badly-tuned analogue television (Schankin et al. 2014). There can be tiny dynamic flickering dots in the entire visual field and other phenomena such as positive after-images. The symptoms are continuous and can persist for many years, and are not thought to be psychogenic. Visual snow is not thought to be a manifestation to be a manifestation of migraine, and the cause is unknown. It occurs in childhood.

**PSYCHOGENTIC SPEECH**

**GLOBUS PHARYNGEUS**

It is rare for a child to present only with a psychogenic disorder of speech. More often a very soft voice, or a return to a ‘babyish’ way of speaking accompany other psychogenic problems. Globus hystericus is a classic symptom of hysteria, but is not a common problem in modern paediatric neurological practice. It is a non-painful feeling that something is stuck in the throat. It has been renamed globus pharyngeus as it is felt that the cause is not always psychogenic (Lee and Kim 2012).

**SENSORY DISORDERS**

The sensory examination can be very helpful in the diagnosis of a PND. An example is the young child complaining of anaesthesia who is asked to close her eyes and to say ‘yes’ if she can feel the subtle touch of cotton wool, and ‘no’ if she cannot feel it. Every time she is touched she says ‘no’. Janet described this sign in an adult woman, but observed that she was ‘simple-minded’ (Janet 1920, p. 169).

A typical presentation of sensory disturbance is the child with psychogenic hemi-anesthesia. There is complete loss of sensation over one-half of the body, with a vertical dividing line running anteriorly from the head down to the pubis, exactly at the midline. (In organic hemi-anesthesia sensation is spared at the midline anteriorly, because of the overlapping dermatomal innervation.) When tested, the child with psychogenic hemi-anesthesia feels nothing at all on one side of the body, but has no ulcers, and no evidence of non-appreciated injury on that side. When vibration is tested one centimetre from the midline of the forehead on the affected side, it cannot be felt at all. When vibration is tested one centimetre from the midline on the unaffected side, it is appreciated normally.

Psychogenic sensory disorders do not follow dermatomal patterns or as Janet observed they follow ‘the popular conception of the organ rather than its anatomic conception’ (Janet 1920, p. 157). In the above example, vibration is conducted through the skull, and, therefore, the unilateral loss of vibration cannot be explained on an organic basis. Another example is total loss of all feeling in the fingers, with the palms having normal sensation. Sensation may be totally lost in a circumferential pattern at the wrist. Although complaining of sensory loss, the child may give vague answers when asked about the exact distribution. Getting them to precisely map out the affected areas on their skin with a pen, and then doing the sensory examination can be very helpful in bringing out
inconsistent answers and revealing a non-anatomical distribution of the sensory changes.

Except for clear-cut examples such as those given above, it is important not to put too much weight on unusual sensory findings in a child. They may have difficulty in describing exactly what is troubling them, or in understanding what the examiner expects.

Pain is a common complaint in PNDs, but is present as an additional feature to the characteristic loss of function. Where pain is the main complaint, the problem is usually regarded as a separate disorder, and the child may be managed by pain specialists, or if the limbs are involved, rheumatologists, rather than neurologists. If intense pain is a problem it is worth considering conditions such as Fabry disease (Politei et al. 2016), and SCN9A mutations (Emery et al. 2015). One of the difficulties is that chronic pain can have a demoralising effect on the person, and this may be misinterpreted as evidence of a psychogenic problem. Another problem is the difficulty in diagnosis of small fibre neuropathies in children, and the lack of knowledge about their frequency. In one study of 41 successive children and young adults with chronic diffuse pain, 59% were found to have ‘definite’ evidence of small fibre polyneuropathy (Oaklander and Klein 2013). Overall, only one patient in the study seemed to have no evidence at all of a small fibre neuropathy. Some of the causes of small fibre polyneuropathy may be helped by treatment, and therefore it is worthwhile keeping this condition in mind, realising that it is probably rare in childhood.

Janet gives an example of the curious nature of hysterical anaesthesia. A 20-year-old girl fell through a glass door sustaining an injury to her median nerve with loss of sensation over her palm. When examined it was found that as well as the organic signs in her right hand, she had hysterical hemianesthesia of the whole left side of her body.

Her doctor asked: ‘How is it, miss, that you come here complaining about an insensibility that affects but a small portion of the palm of your right hand, while you do not even notice the much larger insensibility of the whole of your left side?’ She replied: ‘Be that as you think, sir, I came here to tell you what ails me; it is the insensibility of the palm of my right hand that troubles me, and that of my left side has never given me any trouble. You are the doctor; explain it as you like’ (Janet 1920, p. 163).

**‘La Belle Indifference’**

The term *la belle indifference* was coined by Janet and is regarded as a classic sign of a PND. The patient appears to be unconcerned about physical disability. Pryse-Phillips (1995) defined it as: ‘The lack of emotional expression in the presence of an overt bodily disorder, shown by patients with hysterical conversion syndromes (when it is regarded as culpable) and by stoics (when it is regarded as laudable). Physicians who can tell the difference are called psychiatrists and those who cannot cynics.’ Much more commonly than showing *la belle indifference*, children with PND complain bitterly about their difficulties. They may burst into tears, insisting that all they want to do is to go back to school, or return to sporting activities, at a time when their symptoms make this impossible. When the question of stress is raised, the inevitable response from both the child and the parents is that anyone enduring such suffering would be under stress.

**OVERVIEW OF THE SIGNS OF A PSYCHOGENIC NEUROLOGICAL DISORDER**

Although, on paper, the signs of a PND may appear clear cut and easy to interpret, in practice this is often not so easy. As above from Janet when examining a hysterical hemiplegia: ‘The thing is perfect theoretically, but practically it is much more difficult than is supposed’ (1920, p. 148). The exception is the younger child where there can be an almost comical aspect to the symptoms. An example is the 9-year-old girl described by Tiffany (1907) cited above, who complained that all colours appeared red, except those with a red colour, which looked white. Such symptoms usually evoke a strong caregiving approach from the parents, and at the same time, the parents are usually content that there is no serious underlying disease.

In older children, especially when the problem has been of long standing and many doctors have been involved, diagnosis and management can be very difficult. ‘The presence of weakness, generalised limb pains, weight loss, and depression posed a wide differential diagnosis including malignancy and collagen vascular disease. Many were gaunt and miserable and seemed to be chronically ill’ (Grattan-Smith et al. 1988). Extreme anxiety and distress may reverberate back and forth between the child and the parents. Sometimes, when there is a single localised symptom, such as an immobile and painful limb that is cold and wasted, it may be even more difficult to be sure the problem is psychogenic. Although the signs of PND are reliable, it is by no means always easy to be certain they are present.

When there are a large number of symptoms and signs in someone who is otherwise well, combined with a long list of normal investigations (‘too much smoke and not enough fire’), or if there is a steady accumulation of clinical improbabilities, the diagnosis of PND is considered. However, it can take quite some time for the doctor to be convinced of this, and some families never seem to be able to accept it.

It is well to remember that although there is currently a return to Head’s concept of the value of the positive physical signs, Gould et al. (1986), perhaps influenced by Slater, found these unreliable. In an overview of FMD in adults, Espay and Lang (2015) took the view that neurologists experienced in the treatment of movement disorders can identify ‘a handful of unequivocal and reliably incongruent or inconsistent clinical features in each functional movement phenotype’, and these, when present, ‘allow a clinically definite diagnosis of FMD, regardless of any psychiatric symptom’. Further: ‘No psychiatric symptom, regardless of
severity, can match the specificity of the core phenomenological features associated with each movement phenotype.' However, this comes with a warning: ‘only neurologists with expertise in movement disorders are qualified to recognize the phenomenologic range of FMD as unique and distinguishable from that of complex, and even bizarre, organic movement disorders’.

The current emphasis on the ‘positive’ physical signs is important, and represents a change in emphasis from post-Head, pre-Slater teachings on the diagnosis of PNDs, where the ‘positive’ component of the diagnosis was psychiatric morbidity. In the section on hysteria in Price’s Textbook of the Practice of Medicine (Hunter 1956) is the following: ‘the diagnosis of hysteria must be both negative and positive – negative, by excluding any organic cause for the symptoms; positive, by finding motives and relating the symptoms to them’. In the author’s view, to rely only on the physical signs when making the diagnosis of a PND in a child, carries the risk of misdiagnosis. If, on the initial history, the child seems to have absolutely no reason to develop a PND, then it is wise to proceed cautiously, looking for more evidence of the child being in a stressful situation, and considering rare organic causes.

THE ‘APPELLARENTLY VOLUNTARY’ NATURE OF PSYCHOGENIC SIGNS

A distinction has long been made between malingering where there is a conscious effort to deceive and to gain an advantage, and PNDs where the symptoms are ‘unconscious’. This distinction is far from clear cut, and the label the patient carries may be influenced more by the reaction of the doctor to the patient, than the physical signs.

In 2012, Edwards and Bhatia stated: ‘The key clinical feature that separates patients with FMD from those with organic movement disorders is that the movements have features that one would usually associate with voluntary movement (distractibility, resolution with placebo, and presence of pre-movement potentials), but patients report them as being involuntary and not under their control. There seem to be just two logical explanations for this feature: either movements are deliberately feigned or there must be a brain mechanism that allows voluntary movement to occur but to be experienced subjectively as involuntary’ (Edwards and Bhatia 2012a).

The ‘apparently voluntary’ nature of the signs of a PND has been noted many times in the past. Brodie (1837) observed: ‘In hysterical paralysis, it is not that the muscles are incapable of obeying the act of volition, but that the function of volition is not exercised’ (cited in Stone and Aybek 2016). As discussed above, Page’s impression was: ‘They say “I cannot”; it looks like “I will not”; but it is “I cannot will”’ (Page 1873).

From Wilson (1911): ‘Thus I have seen a patient with a complete hysterical hemi-anæsthesia stand beside her bed looking out of the ward window, and at the same time fumbling in the drawer of her locker, with her anaesthetic hand to find a hairbrush, which she did quite easily. I have noted a patient with profound paraplegia of the typical hysterical sort move her immobile limbs while she lay half-asleep. I have observed another patient, whose hysterical right arm hung helpless by her side, move it briskly to her face to avoid coughing in front of the physician. In each instance, the patient offered no explanation of the incident, but simply repeated her tale of inability to move the limb, or of complete loss of feeling. These facts are of great interest and their explanation is difficult.’ Wilson concluded: ‘It appears to me the movements are volitional only in appearance, and that the conscious ego does not participate therein.’

Sir Francis Walsh (1952) in his inimitable style, distinguished malingering from hysteria. ‘The malingerer is one who with full moral responsibility for her acts and with full awareness produces bodily disabilities. She is an actress who knows she is acting. In the hysterical subject, it is probable that neither full responsibility nor full awareness is always present. The latter certainly tends to diminish, for the hysterical often acts as an actress who becomes progressively convinced of her own acting and may ultimately come to join the audience. Current theories of the genesis of the psychoneuroses require that the psychological processes underlying them should be below the threshold of consciousness, and the clear evidence to the contrary sometimes provided by clinical experience has been ignored or suppressed in the interests of theory.’

From Brain (1955): ‘It follows that the hysterical symptom is always the expression of an idea in the patient’s mind. Thus hysterical aphonia expresses the idea “I have lost my voice”, hysterical paralysis the idea “I cannot move my limb” and so on. This fact is of great diagnostic importance, for it is impossible that the patient’s idea of a symptom should correspond with a similar symptom produced by organic disease, and the resulting discrepancy renders possible the diagnosis of the one from the other’.

From Hamilton Bailey’s surgical text comes the following in discussing hysteria affecting joints: ‘Gentle palpation may appear to cause intolerable pain, but if the attention is distracted, considerable pressure will pass unnoticed’ (Bailey and Love 1959).

Whatever the underlying mechanisms that are in play, it is the ‘apparently voluntary’ nature of the signs that is most useful in making the diagnosis of a PND. It answers Slater’s question: ‘What are the positive signs of “hysteria”? Unfortunately Head could not describe any common characteristic by which these signs could be recognised, and he dealt with them by enumeration … What is given is a list, which might be enlarged without limit’ (Slater 1965). The ‘apparently voluntary’ nature of the signs can be applied to the ‘kaleidoscope’ of manifestations of PNDs, and is a guiding principle in approaching the ‘lists’ of signs of psychogenic disorders. It explains how for so long adult neurologists have been able to make the diagnosis of a psychogenic neurological disorder without relying on the psychiatric history.
RED FLAGS

For many patients and doctors the greatest ‘sin’ in medicine is to misdiagnose a person as ‘psychogenic’ when in fact they have an ‘organic’ disease. The impact of Slater’s claim, that a large number of patients diagnosed with hysteria actually have an underlying disease, has been discussed above. In a sense the pendulum has swung to the other extreme, and there is now a view that the positive signs of a PND are specific, and misdiagnosis is unlikely. For example in a large adult study, at 19 months follow-up of patients with ‘symptoms unexplained by organic disease’, only four out of 1030 patients (0.4%) had acquired an organic disease diagnosis that was unexpected at initial assessment, and plausibly the cause of the patients’ original symptoms (Stone et al. 2009).

There are a number of circumstances where the diagnosis of a PND should be made with particular caution and only after careful investigation. The first of these is when the patient is under the age of 8 years. Rivinus et al. (1975) reported 12 children who over a 12-month period were admitted to a single institution, and had initially been diagnosed as having a psychiatric disorder, but were then found to have life-threatening neurological problems including spinal tumours, metachromatic leukodystrophy, Batten disease and subacute sclerosing panencephalitis. At the time of their initial ‘psychiatric’ presentation, two of these children were 8 years old and a further seven were younger than this. The reason for caution in the younger child, is that a certain level of maturity is required before children can exhibit the symptoms and signs of a PND. As Taylor (1986) has observed: ‘Finally hysteria can only be promoted by persons with the necessary social skill or by those that derive that skill through their allies. This constraint, among others, precludes young children from hysteria.’

There are also certain symptoms that should always raise concern. Particularly if the child is 10 years or under, back pain, back stiffness and torticollis are all symptoms that require careful attention. Two of the patients in the Rivinus series misdiagnosed as hysteria, had spinal cord tumours, and presented with back pain or abnormal spine postures. In a study of Grattan-Smith et al. (2000), three children with serious spinal cord problems had been initially diagnosed as having hysteria by referring doctors. Another child had back pain that was after admission found to be psychogenic in origin. The stories of two children in this series highlight the importance of careful physical examination in making a diagnosis. An 11-year-old girl who was initially diagnosed as hysterical, had leg weakness and sensory signs from spinal cord trauma after a ‘human pyramid’ fell on her. This girl had every reason to develop a psychogenic disorder. Her father had died in a work-related accident 2 years earlier, and her uncle was paraplegic after a motorcycle accident. In contrast, a 12-year-old with a very worrying story of progressive back pain and weakness, was an extremely successful, high-achieving girl who had no obvious reason to develop a psychological illness. It was the physical signs in the first girl that led to a diagnosis of spinal cord injury, and the lack of signs and the ‘psychogenic’ gait that led to a diagnosis of a psychogenic disorder in the second girl, who danced 5 days a week and was a ‘perfectionist’ who hated making any mistakes. With treatment, the second girl made a full recovery.

The examination of the child with back pain should include a careful search for a motor or sensory level, with the sensory testing including the buttocks and perineal region, and plantar surfaces of the feet. The ankle jerks should not be checked casually. If anal reflexes or the bulbocavernous reflex are to be tested, it is obviously important to explain the reason to the child and family, and sensible not to do this without a member of the nursing staff or colleagues present.

Although non-specific back pain is becoming an increasing problem in adolescents (Shah and Saller 2016), nevertheless it is a symptom to be respected especially in the younger child. Again, the lessons from the past should not be forgotten, and this paragraph ends with words of warning from two of the greats. ‘Back pain, so common in adults, in childhood is rare; if it occurs before 10 years of age, it is due to an organic lesion almost without exception’ (Apley 1976). ‘Indeed spinal cord compression is an even more serious emergency than raised intracranial pressure, and this possibility must always be present in the mind of paediatricians, while the diagnosis of acute myelitis, “hysteria” or malingering should never be accepted before cord compression has been clearly excluded’ (Aicardi 1992, p. 831).

Urinary retention has been described as a psychogenic symptom in adults (Hoeritzauer et al. 2016), and rarely in children who have suffered severe abuse (Parmar and Roberts 2013; Iskandar and Vance 2015), where it is usually associated with other psychogenic symptoms. As a general rule urinary retention, or the sudden onset of severe urinary and faecal incontinence are symptoms that point to an organic cause, and only after very careful examination and investigation, and in the presence of gross psychopathology, should a psychogenic cause be considered.

There are other situations where a psychogenic misdiagnosis is more likely to be made. These include the child who screams, and will not stay still or co-operate because of pain. A child who has had multiple psychogenic problems in the past, is at particular risk if he or she develops an organic problem. Families who are highly dramatic, and give colourful and emotionally charged descriptions, are also at risk. As Slater (1965) observed: ‘People with, say, a histrionic temperament naturally lend the stamp of their personality to their symptoms, whether they are suffering from an organic or neurotic disorder … Unwittingly, inevitably, from his very nature, the patient applies the hystero-diagnostic stimulus; unwittingly inevitably, from the long process of conditioned training through which he has gone the doctor reacts with the hystero-diagnostic response.’ As discussed above, movement disorders such as dystonia can produce what appear to be bizarre symptoms and signs which can be easily mistaken for a psychogenic problem.
WHAT IS THE UNDERLYING CAUSE OF A PSYCHOGENIC NEUROLOGICAL DISORDER?

Any discussion of an underlying cause of PNDs has to take account of the many different therapies that have apparently helped or ‘cured’ patients over the last 100 or more years. A short list includes (1) ‘rest cures’ (Weir Mitchell 1877; Playfair 1881; Saville 1907); (2) various forms of electrical stimulation, transcutaneous electrical nerve stimulation and transcranial magnetic stimulation (McWhirter et al. 2015); (3) electroconvulsive therapy (Russell 1950); (4) abreaction, which involves interviewing patients after they had been given a drug, typically a barbiturate (Poole et al. 2010); (5) exercise (Dallocchio et al. 2010), including the ‘training camp method’ (Orbison 1925); (6) hypnosis (Brown 1918; Deely 2016); (7) antidepressant therapy (Voon and Lang 2005); (8) psychoanalysis (Macalpine and Ross 1956); (9) wrist braces and other physical treatment (Sauerhoefer et al. 2011); (10) physiotherapy (Nielsen et al. 2015); and (11) placebo (Scola et al. 2014; Rommelfanger 2016). Few if any of the original papers would be regarded as of sufficient standing to be part of a Cochrane review, but this is the nature of PNDs, and we have to work with what is available.

Wilson (1911) reviewed the many theories active at that time as to the cause of PNDs and observed: ‘The mere enumeration of these conflicting hypotheses may overwhelm the reader with a deep sense of despair at their hopeless dissimilarity; and he may reasonably fear that finality is as far off as ever. But let him not be unduly distressed.’ Wilson then points out that what the many theories have in common, is that patients seem to respond to treatment whatever it is, and this makes the treating doctor sure he has the answer to the problem. ‘Odd as it may appear, many of these contradictory features have one feature in common. Not only are the respective originators alike in the earnestness of their advocacy of them, but there is a curious similarity in their appeal to their own clinical experience subsequent to the adoption or enunciation of their own particular theory, and in their resort for substantiation in its virtues to the results of treatment.’

Wilson continued: ‘To the individual who is not so absorbed in science as to lose his sense of humour it may seem that Hysteria, while she responds so nobly to the appeals of the advocates of these various theories, is quietly smiling in her sleeve. As of old the ascetic and the epicurean, the celibate and the polygamist, the socialist and the monarch by divine right turned to the pages of Holy Writ for support of their particular ways of living and views on life, and found it therein, so the exponents of sexual theory, the suggestion theory, the sleep theory, and the “hysteria-only-a-symptom” theory, alike appeal to experience for confirmation of their opinion, and find it.’

Wilson commented on the influence of the treating physician. ‘It is not merely that his hypothesis is apt to colour the physician’s way of looking at a case, but also that in some obscure and little understood manner the patients come in a sense to respond to his hypothesis, so that the wider his experience, the greater is the apparent confirmation of the truth.’

More often than a single method, it is a combination of therapies that have been used. Saville’s regime (1907) consisted of strict bed rest, removal of patient from their previous surroundings, good food, massage, electrotherapy, hydrotherapy and psychotherapy. Depending on the circumstances, Saville would also use unpleasant treatments: ‘Apomorphine hypodermically is, however, the most valuable remedy we have for the prompt cure of severe and recurrent hysterical convulsions; it produces copious emesis and the storm clears up like magic.’

‘NEUROBIOLOGICAL’ THEORIES

‘The student of the history of such an old-world disease as hysteria cannot fail to be impressed with the fact that the point of view from which it has been considered has varied greatly from one epoch to another, and that this point of view may be taken to be a reflex of the mental outlook of the age in which it has found an expression’ (Lancet 1910).

There is currently a great deal of interest in neurobiologic approaches to PND. These look at how the symptoms and signs of a PND can be implemented within the anatomy and physiology of the brain’ (Edwards 2016). Perez et al. (2015) summarised recent work and found that ‘convergent preliminary findings suggest alterations in neurocircuits mediating emotional processing, regulation, and awareness (ACC, vmPFC, insula, amygdala, vermis), behavioural inhibition and cognitive control (inferior frontal gyrus, DLPFC, dorsal ACC), self-referential processing and perceptual awareness (PCC/TPJ, precuneus), and motor preparation and coordination (SMA, cerebellum). Striatal-thalamic components of prefrontal-parietal networks may also play a role in pathophysiology’. It is the view of Perez et al. that the cause of PND, is not a psychological disturbance but brain-based dysfunction: ‘Improved understanding of the biological mechanisms underlying these conditions (and disorder subtypes) will improve recognition that these patients suffer from a biological, functional brain-based disorder and will help reduce stigma associated with this diagnostic category.’

Neurophysiological and imaging techniques have demonstrated differences in the brain of patients with PND when compared to controls. The subject is too vast to cover here but the warning of Edwards (2016) seems apt. ‘If we are studying a particular illness and an area of the brain “lights up” in a functional imaging study in our patients and not in controls, it is easy to start thinking that we have found the bit of the brain that is causing the illness. It is a short step from there to
saying that illness \( x \) is damage/dysfunction of brain area \( y \). This naïve reductionism is attractive but very flawed.’

The difficulties inherent in applying neurophysiological techniques to PND, (and of PND in general), are well shown by the report of Ramos et al. (2015), where two young women with childhood-onset psychogenic dystonia were treated with deep brain stimulation under the misapprehension that they had an organic problem. Even in retrospect, no difference was found in the rate of firing of intraoperative microelectrodes inserted in the globus pallidus internus in these patients when compared with the firing rates of patients with DYT1 dystonia. One of the patients was implanted at age 18, and within 6 weeks had a remarkable improvement in her dystonia and tremor and was able to walk. ‘Improvement persisted and she was able to walk across the stage for her high school graduation and dance at her wedding’. However, 4 years after implantation, she deteriorated markedly. It was then noted that her symptoms were unchanged whether the stimulator was on or off. In both patients, the stimulators were removed and they became essentially symptom free after intensive cognitive, behavioural and physical therapy. The authors concluded: ‘Although caution must be exercised in interpreting our results, it does highlight that there is still no neurophysiologic parameter, and thus no reliable diagnostic test, capable of differentiating between organic and psychogenic dystonia. As such, the diagnosis remains clinical and can be challenging for complex cases.’

Papers on the neurobiological approach have dealt with complex concepts that have philosophical underpinnings such as the sense of agency, attention (a subject of interest going back more than 100 years to William James, and discussed by Paget in 1873), and beliefs and expectations (Edwards 2016). Bayesian theory has also been incorporated into the discussion (Edwards et al. 2012b). These concepts are of great interest, but thus far have not been formulated in such a way that they can easily be incorporated into a discussion of the diagnosis with the child or parents. Edwards (2016) also believes that neurobiological approaches are only part of the solution. ‘A one-dimensional approach to FNS (functional neurological symptoms), for example, a purely psychologic interpretation of symptoms and mode of treatment, or one that highlights neurobiologic mechanisms while ignoring the level of cognitive and psychologic experience, is doomed to failure.’

‘PSYCHOLOGICAL’ THEORIES

As discussed above, Freud’s theories have recently been heavily criticised, and his concept of conversion of emotional difficulties into physical symptoms, is no longer readily accepted. ‘There are, however, theories that attempt to explain PND on a psychological basis. Again, there is only space for a brief review. Rofé and Rofé (2013) have proposed a ‘Rational-Choice Theory of Neurosis’ (RCTN) which ‘incorporates Freud’s idea, implicitly expressed in his theory, that neurotic disorders are, in fact, rational behaviors’. In this theory repression is used as ‘a conscious coping mechanism which deliberately eliminates threatening stimuli from attention through the employment of distractive maneuvers’. The patients ‘consciously and rationally choose a neurotic behaviour which heavily occupies their attention to the extent that they become unaware of their stressor’. Contrary to psychoanalysis, in this theory, the symptoms arise in response to current stressors, rather than historical events.

According to RCTN the choice of a specific conversion symptom is determined by three main principles (1) needs; (2) availability; and (3) cost-benefit analysis. The concept of ‘needs’ is that patients usually choose a specific symptom that enables them to gain relief from a stressful situation. As an example, aircrew in World War II with psychological disorders were most likely to develop visual disturbance, which meant they could not fly. Availability is the use of previous experiences to develop a symptom, and is similar to Taylor’s concept of a ‘model’. In discussing ‘cost-benefit analysis’ Rofé and Rofé propose that ‘human behavior is based upon rational calculations of cost-benefit in the interest of maximizing personal utility’.

Rofé and Rofé propose: ‘The choice of a specific conversion symptom may be unconscious or spontaneous with no prior planning. However, the actual implementation of this choice is fully under conscious control.’ ‘This is almost immediately followed by the activation of psychological mechanisms which make the patient unaware of that choice, and then preserve this unawareness. In the case of hysterical paralysis, the patient observes that the limb is not moving, and at the same time has a feeling of loss of control of the limb, consolidating the belief that there is a physical problem. This evidence will lead to a self-deceptive diagnosis of illness where patients believe that there is something physically wrong with them that are beyond their control.’ As a result of the intense preoccupation with the symptom and the self-deceptive beliefs, the patient becomes unaware of the voluntary adoption of the symptom.

The cost-benefit principle also explains why people subsequently abandon their symptoms because of either reduction in the benefit or an increase in the cost. ‘As specified before, punishment procedures, such as withdrawal of attention or the application of noxious stimuli, motivate patients to abandon their conversion symptoms. While behaviourists account for the efficacy of this therapy by learning concepts, RCTN attributes it to the disruption of the cost-benefit equilibrium of the symptom. Once the symptom ceases to be beneficial, patients are motivated to consciously abandon their symptom.’ They cite a case history of Jung. ‘For example, when Carl Gustav Jung (1963) informed a middle-aged female patient, who had been suffering from hysterical paralysis for many years, that he was going to hypnotise her, the patient immediately fell into a deep trance, before the therapist started the process. She talked without pause for over a half-hour, resisting Jung’s attempts to awaken her. Soon afterward she declared herself cured, threw away her crutches and proceeded to walk … From RCTN’s standpoint, it seems likely that after so many years of suffering from the fake symptoms, the stressor was either removed or
she adjusted to it. The symptom became a burden and Jung provided her with the deceptive excuse required to abandon this behaviour."

Although RCTN provides an explanation for the success of so many different treatment methods with PND, it carries with it a tone that many would find unattractive. It is reminiscent of Palliser’s Mr Pentecost: ‘Self interest is all that drives us Mr Pentecost went on: “But we are infinitely resourceful in finding ways to disguise this truth from ourselves and others, and hence arises the prevalence of hypocrisy and self-deception” (Palliser 1991).

Perhaps the last word on the difference between ‘neuro-biological’ and ‘psychological’ theories should go to Janet. ‘Thus, I shall perhaps surprise you by telling you that there is no opposition between the definitions that gloriously entitle themselves physiological and those that modestly call themselves psychological’ (Janet 1920, p. 321).

TAYLOR’S APPROACH

The great English neuropsychiatrist David Taylor has provided a way of looking at the evolution of PNDs in children which the author has found useful in practice (Taylor 1986). Taylor’s position is: ‘I believe that hysteria is generated as a defence mechanism and propagated as a consensual phenomenon, as is magic. Like magic it has no real properties beyond belief.’ Further: ‘There is little evidence to support the idea of psychopathology in children with hysterical symptoms.’ ‘People exhibit distress through whatever scope is left to them. The body speaks what the tongue cannot utter.’

Taylor outlines the elements of a PND: (1) The first requirement is the child is in a predicament ‘which is intolerable but for which all apparent solutions are blocked’. Sexual abuse in the family is a well-known example, but there are equally painful alternatives. (2) The second component is an ally who helps to promote the sickness’. The ally acts ‘like a manager; he too may have been innocently trapped, or else have his own psychopathology’. The ally will vigilously defend the right to be sick’ and pursue disease explanations relentlessly’. The third component is a model of the sickness which has to be available, whether current of historical, real or contrived, chronic or ephemeral’.

In this formulation doctors can be a decided problem when they become the ally. ‘Doctors in particular, and other health care workers to some extent, can provide well for all these elements. They can block alternative explanations by patients, or by failing to take an adequate history of their predicament fail totally to discern it. They are powerful allies in sickness promotion, and can be sucked into the system quite unwittingly, especially if they have an investment in a biomedical diagnosis. They provide a variety of models and can offer suggestions which improve the credibility of the sickness.’

Taylor acknowledged his views are, in part, similar to others including Kretschmer and Slater. ‘Their view is that hysteria is a social construction set up in the doctor–patient relationship.’

Others have commented on the role of the ally. Walshe (1952) notes, ‘the hysterics requires a human background of family or of community, with which to interact. Thus an entire family or household may be influenced by a family member and come unwittingly to minister to the neurosis and build it up’. Fahn and Jankovic in discussing adults with psychogenic movement disorders observed: ‘Many of the affected individuals have a devoted spouse who responds readily to their pressing needs.’ From Sim (1966): ‘hysteria is a form of behaviour or communication designed to show society the distress of an individual or to elicit society’s support, and is not a form of private meditation but generally a public display’.

‘NO EVIDENCE OF A PSYCHOLOGICAL PROBLEM’

In the retrospective review of Grattan-Smith et al. (1988), the families had two broad patterns of behaviour. Thirty families (58%) were found to have an anxious home environment, with pervasive fears of loss and physical illness. In contrast, in 11 families (21%), there was a gross breakdown in family relationships with parents and children in open conflict. The symptoms were generally more obviously ‘psychogenic’, and the diagnosis more easily made in this second group.

It is with the first group of families where difficulties with diagnosis and management particularly occur. In both adult and paediatric practice, it is common experience for a person to be diagnosed as having a PND, only to then go and see a psychologist or psychiatrist, and be told that there is no evidence of any psychological disorder that might cause their symptoms. The ‘all clear psychologically’ verdict appears to result from a strange irony, that although much of what Freud wrote has been discounted, there is still a search for Freud’s ‘traumatic scene’, one of his earliest concepts and a scene that he, himself, had difficulty finding. What psychologists and psychiatrists are saying is that the person does not have an obvious severe psychological problem, and this is usually correct.

The two recent surveys of PND in children also do not show a picture of severe psychological disturbance. Antecedent stressors were reported in 62% of children by Kozlowska et al. (2007), and 81% by Ani et al. (2013). In the paper of Ani et al., the most common antecedent stressor was bullying at school. What about the psychological function of the children? In the study of Ani, 78% of children, with data on psychiatric history available, had had no mental disorder prior to the episode of conversion disorder. Of those with a premorbid psychiatric diagnosis, anxiety disorder was reported in 21 out of 200 (11%), and depressive disorder in ten out of 194 (5%). How do we justify diagnosing such children as having a psychological disorder? Especially when as Slater (1965) correctly asserted, ‘trouble, discord, anxiety and frustration are so prevalent at all stages of life that their mere occurrence near to the time of onset of an illness does not mean much’. As Freud in 1912 observed, the common cause is an accumulation of lesser stresses: ‘In ordinary hysteria instead of one
big trauma we not seldom find many partial traumas, grouped causes which can be of traumatic significance only when summarized and which belong together in so far as they form small fragments of the sorrowful tale.’

A common predicament currently encountered is the girl who is simply doing too much. She may be one of the top students in her class, the class captain, excel at multiple sports, do dancing or gymnastics, drama or debating and play one or more musical instruments. Often she has taken all this on willingly, and it is not due to parental pressure. Over time the need for continuous perfection in so many areas becomes too much, and sickness is the only defence. A minor injury or illness tips her over the edge into a prolonged illness. These children can exhibit the same determination and persistence in being sick as they do in all other areas of their life. Grattan-Smith et al. (1988) (looking at children mainly from the 1970s when life seemed a lot easier) identified a ‘difficult’ subgroup of children who presented particular problems in both diagnosis and management. They were generally ‘good’ children, serious minded, compliant and perfectionistic, who came from families with high expectations of them and were anxious about illness.’ Leslie (1988) made the same observation in a study of 20 children (13 girls and seven boys). An interesting finding, however, was the extreme conscientiousness not to say perfectionism of at least half of the children, and it was this characteristic which could have led paediatricians to agree with the families that such exemplary children who were doing so well academically and socially and who had had no previous psychiatric histories could not possibly have had psychiatric problems.’ Families with high levels of perfectionism will often vehemently deny that anything is less than perfect at home. A brief visit to a psychologist or psychiatrist, particularly if that person has a ‘neurobiological’ focus, is unlikely to do anything but confirm what the family already believes.

There are, of course, many other predicaments including physical or sexual abuse, but these seem to be a relatively uncommon cause in recent reports of psychogenic disorders of childhood.

THE IMPACT OF DELAYED DIAGNOSIS

In the literature on PNDs, emphasis is often placed on the role of delayed diagnosis and excessive investigation in prolonging the illness. However, some families simply refuse to accept that the diagnosis is possible, even if informed at the very beginning of the illness. In the study of Dale et al. (2010), of 12 children who presented acutely with PMD, three families refused to engage with psychological therapy at all. Further: ‘Despite resolution of the movement disorder in many participants, five of the children experienced multiple relapses in the context of families declining treatment of comorbid anxiety or depression, or being unwilling to address ongoing psychological stressors. ‘Three had intractable PMD over a period of 6 to 18 months.’

The concept that it is simply a delay in diagnosis that is responsible for some children with PMD having a prolonged illness, satisfies neither experience nor reason. ‘Much can be made of the role of excessive investigation, contradictory medical opinions, and failure of early recognition of the problem in this sort of prolonged course. It may be equally argued that these children were sicker, their predicament worse, their allies stronger, and their nature more obstinate’ (Grattan-Smith et al. 1988). If there is no resolution of the underlying predicament, then just identifying the problem as psychogenic in nature, may not help the child at all. Rather the child may be worse off, being no longer protected by the symptoms, and have no option but to develop new ones.

**PSYCHOGENIC? FUNCTIONAL? WHAT IS THE CORRECT NAME?**

‘The progress of medical knowledge has been so greatly hampered by persistent use of the two terms ‘organic’ and ‘functional’ that it is high time they should be discarded for ever’ (Wilson 1930).

The second task in seeing a child with a PND is explaining what is meant by the diagnosis. Controversy as to what is the correct name to be used goes back hundreds of years, as has been discussed above. Despite Briquet’s warning that physicians should not amuse themselves by wasting their time in arguing over words, the choice of word is important. The use of an unacceptable name can bring about an immediate halt in proceedings. It seems logical, therefore, to use a name that is, at least, neutral. Ideally, the meaning of the word should be easily understood by the child and family, and contain within it an indication of cause, and also the path for treatment.

Phrases such as ‘symptoms unexplained by organic disease’, or ‘medically unexplained illness’ have been tried but were found wanting, as they had no real meaning, except focusing on what the patient does not have. It has recently suggested that ‘functional’ should be the word used, and is to be preferred to, for example, ‘psychogenic’ (Edwards et al. 2014a, 2014b; Fahn and Olanow 2014; Ganos et al. 2014; Jankovic 2014; La Faver and Hallett 2014). As discussed above, ‘functional’ is an old word going back at least to Charcot. At that time it was used in the sense of an organic disease that had not yet revealed itself to scientific methods. Subsequently functional was used in the way we use psychogenic. In a recent review of the use of the word, the conclusion was that ‘functional’ is ‘a simplifying euphemism allowing neurologists to use one term to mean one thing to colleagues and another to patients’ (Kanaan et al. 2012). There are also practical issues because of the multiple uses of ‘functional’. In December 2016 a PubMed search for ‘psychogenic neurological disorders in children’ resulted in
589 ‘hits’. For ‘functional neurological disorders in children’ the number was 17,655 with most not relevant to the purpose of the search.

‘Psychogenic’ is the word that has been used throughout this chapter, but it also has problems. According to Lewis (1972) the word was introduced into psychiatry in 1894 by Robert Sommer. The view of Lewis was: ‘Robert Sommer rendered psychiatry a disservice when he coined the word “psychogenic” and so gave currency to a confused but speciously attractive and convenient concept. The subtle arguments of French and German disputants have shown it to be at the mercy of inconsistent theoretical positions touching on the fundamental problems of causality, dualism, and normality. It would be as well at this stage to give it decent burial, along with some of the fruitless controversies whose fire it has stoked.’ More recently Edwards et al. (2014a) in promoting the alternate ‘functional’ criticise ‘psychogenic’ as ‘a term that defines the disorder with regard to a proposed aetiology, which is poorly defined and is not supported by current evidence’.

The current situation is not substantially different to the time of Clarke who in 1893, in respect to ‘hysteria’, observed: ‘The ancient meaning of the word and the ideas connected with it have been finally abandoned, and as yet no substitute for it has been found.’

It could be argued that no word will ever satisfy both patients and doctors, when there is centuries-old uncertainty about exactly what is happening when a ‘psychogenic’ neurological disorder occurs. The final choice may have to be the ‘least-unacceptable’ word. In this setting, the concept of the child being under stress, and the diagnosis of a ‘neurological disorder induced by stress’ is a useful formulation.

‘STRESS’

Although Webster’s Dictionary gives 13 different meanings to the word ‘stress’, most children and families have a good understanding of what stress means. Kostenius and Öhrling (2008) surveyed the concept of stress in 23 children (12 boys and 11 girls) between 10 and 12 years. These children listed multiple situations when they experienced stress. These included when there was not enough time to compete an allocated task; when they felt they were not good enough; when they worried what others would think about them if they revealed their real self; when they felt they were being run by others; when they were under pressure to perform; and when they felt powerless and had to unwillingly conform to other people’s decisions. All this fits well into Taylor’s concept of a predicament. The children also recognised that stress generates more stress, and can produce a downward spiral if not handled well, and that the stress of other people can spread and infect them. They also acknowledged the importance of some degree of stress for peak performance. As one child said: ‘it depends on how stressed I am … if I am very stressed I get very little done but if I am a little stressed I get more done’.

In those children who seem to be previously well adjusted, and develop a PND in the context of doing too much, the concept that the problems have arisen from external stress, can be helpful in both diagnosis and management. It will be discussed in more detail below, but the child is told that there are multiple individual areas of stress acting upon them. Alone they would not cause a problem but when combined, especially if the child then becomes sick or has an injury, they become too much.

Another advantage of stress as a concept is that chronic severe stress can cause structural changes in the brain (McEwen 2012; Eiland and Romeo 2013). A diagnosis of stress as the cause of the symptoms does not require an immediate commitment into either the ‘neurobiological’ or ‘psychological’ camps.

There is an adult study where 33 patients with FMD were studied and found to have salivary cortisol levels no different to normal controls (Maurer et al. 2015). Based on this lack of elevation of cortisol levels, the authors concluded ‘current stress levels are not altered in patients with functional movement disorders’ and that ‘the insistence on heightened stress levels in these patients is unjustified’. However, 76% of these patients had already had symptom for more than a year when studied. It seems simplistic to assert that measurement of cortisol levels, even over a 2-day period, years after the onset of symptoms is an accurate measure of stress levels when the symptoms commenced, which is obviously the critical time. The patients were also admitted to hospital for the testing, and so away from their usual environment. Finally, it appears unlikely that such a complex process as stress is going to readily yield itself to routine laboratory tests.

INFORMING THE CHILD AND FAMILY OF THE DIAGNOSIS

For most paediatric neurologists, the task of diagnosing a PND is difficult enough, and they do not wish to be involved in the treatment of the child. This view is summarised by Ford (1960): ‘This is a psychiatric problem and if the neurologist is not prepared to undertake this responsibility, he should place the patient and the parents in the hands of the best psychiatrist available. It is my custom to follow this course and to wish both the patient and the psychiatrist the best of luck.’ However, the paediatric neurologist has a crucial role in informing the child and family of the diagnosis.

The discussion usually occurs after investigations have been done. ‘Taking one look’ at the child and then diagnosing a PND, will not convince many parents. They have read too many stories about the misdiagnosis of children with brain tumours, and ‘MS’, in the papers and on social media to simply accept the opinion of a doctor, except in the most obvious of cases. It is important to get all planned investigations done as soon as possible, and not have them strung out over weeks. These investigations have an important role in persuading the child and the family that the symptoms are being taken seriously, and there is no evidence of an underlying disease.
If, after the tests have come back negative, the possibility of a PND is raised for the first time, then a suspicion can easily develop that this diagnosis is being suggested because the doctor does not know what is wrong - 'it doesn't make sense so it must be in her head'. Therefore, at the time of ordering the tests when a PND is suspected, it is important to say to the child and family that there is a good chance that the cause is stress, and if this is the case it will be a good outcome, as a complete cure is possible.

There are many different ways of having the discussion and the following describes just one approach. To be effective, plenty of time has to be available as the first reaction of the parents is often shock and incomprehension, followed by many questions. The first step is countering suspicions that, cloaked in medical professionalism, you are accusing the child of 'faking it', something that siblings and other children have often already suggested. The child is seen with the parents and, given that most often the child is 10 years or older, the discussion is directed towards the child with the parents listening and free to ask questions as the discussion proceeds.

The 'script' has been described previously (Grattan-Smith and Dale 2016), and is reproduced to give an example of an approach that has proved effective. As discussed above, the term 'stress-related' is preferred to 'psychogenic' or 'functional'. This approach applies in the common setting of the high-achieving child who is doing too much. If the cause of the PND were severe abuse than obviously a different approach would be needed.

"As I have previously suggested, your problems are very likely to be caused by stress. For more than a hundred years doctors have recognized that the signs and symptoms you have, indicate that you are under stress. This is good news. There are many diseases that leave children severely disabled or that are fatal, and here there can be a complete recovery.

I commonly see children with such reactions. From my own experience and many articles written by doctors, it is clear that children with these reactions are not disturbed or 'crazy', and are not being abused at home. Rather, they are usually high-achieving kids who are very thoughtful and considerate towards other people. As the same time they tend to want to keep their feelings to themselves so as not to worry others, especially their parents.

Over a period of time the child comes under the pressure of multiple stressful events. Each one by itself is manageable but they build up and act all together. The child tries to ignore them and keep them out of the conscious mind, but they are there. There is then often an injury or illness that would usually cause a problem that would only last a few days. However, the stress then takes over. The symptoms then last much longer and are much more severe than they otherwise would have been. It can take some time to get back to normal, but full recovery is expected.

One way of looking at this is that the body knows it is under pressure and as a defence against stress 'shuts down' to bring a change in the situation."

The discussion usually includes many questions from the parents (and child), often initially with complete disbelief that a child previously so high-functioning could be brought down by stress. At that time historic examples such as Horatio Nelson and Florence Nightingale can be discussed as people who were very high achievers despite being subject to stress. The concept of the necessity of stress for peak performance is also covered, accompanied with the advice that stress is 'a good servant but a poor master'. What is needed is some fine tuning, not a drastic change. The child is told that it is important to always put in a full effort, but it is impossible to be perfect at all times. Depending on how the meeting is going, giants of the past can be cited, such as, 'perfect is the enemy of good' (Voltaire) or 'better a diamond with a flaw than a pebble without' (Confucius).

This discussion is aimed at putting the concept of external stresses being brought to bear on a sensitive child before the child and family. It is emphasised that children with problems due to stress are often highly competent, good children who try to keep their feelings to themselves, and do not want to worry their parents. The children try to ignore the stress, but it has to come out in some way, and this takes the form of physical symptoms such as weakness and pain. There is no need to try to win every point in the discussion. Nor should it be expected that the child and family will agree with you immediately. Some families seem never to agree, but in the study of Ani et al. (2013), 'over 90% of families had some level of acceptance for a nonorganic explanation'. Depending on how unwell the child is, and the response to these suggestions, plans can then be made for future management.

Although in PND the apparently voluntary nature of the signs is important in making the diagnosis, a discussion with the child and family of whether or not the signs could be ‘deliberately feigned’ is a recipe for certain disaster. Likewise, reference to Taylor’s concept of an ally is likely to result in the parents storming out of the room, dragging their child behind them.

The question of how ‘truthful’ you should be in such a discussion is difficult. Gupta and Lang (2009), for example, in dealing with adult patients with psychogenic movement disorders suggest not telling the patient the problem is ‘psychogenic’: ‘To maximise treatment compliance, it should be acknowledged that the patient has a movement disorder (i.e. a form of tremor, myoclonus, or dystonia) and a biological explanation provided.’ This is not a new approach. Brain (1963) quotes Edward Jordon who in 1601 wrote: ‘So that if we cannot moderate these perturbations of the minde, by reason and persuasions, or by alluring their mindes another way, we may politikely confirmhe in their fantasies, that wee may the better fasten some cure upon them.’ In World War I, Hurst and others performed mock operations on soldiers suffering from ‘shell shock’, and produced dramatic cures (Hurst 1917). Myers (1919) condemned this ‘therapeutic lying’. ‘Whatever the method of psychotherapy adopted the full truth is not always possible; explanations have to be couched in terms fitted to the mentality of the patient. But
downright lies are to my mind never necessary and deserve vigorous condemnation, especially when carried over into needless and possibly harmful action.’

The approach suggested above using the concept of stress, employs a word well understood by children and families, and in that word can be found both the cause and remedy of the problems. Although this approach contains elements of Freud’s concept of conversion which has been criticised, nevertheless it is usually accepted by children and their parents and does not stray too far from the ‘truth’. It avoids the moral judgments implicit in terms such as unconscious, conscious, factitious, and malingering, and views the signs and symptoms neutrally, as a signal of distress, allowing plans to be made for the best way to help the child. By identifying stress front and centre as the cause, it will hopefully prevent the establishment of a recurrent cycle of stress-related illnesses in the child.

Stone and Edwards (2012) have suggested that as part of such a discussion the patient should be shown the reasons their signs are considered psychogenic, and as an example went over Hoover’s sign with a 42-year-old man with psychogenic leg weakness. The result was pleasing. At a follow-up visit he explained that understanding the physical basis of the diagnosis had made a dramatic difference to him. He and his partner now had confidence that it was the correct diagnosis. By dealing calmly with anger, staying logical, and seeing the signs and symptoms neutrally, a signal of distress, allowing plans to be made for the best way to help the child. By identifying stress front and centre as the cause, it will hopefully prevent the establishment of a recurrent cycle of stress-related illnesses in the child.

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HOSTILE REACTIONS

Hostile reactions are common when the diagnosis of a PND is made, and the treating doctor has to accept that the reactions are often illogical. For example, in the study of Macalpine and Ross (1956), both patients became angry when told their problems were psychological, and they needed neither sympathectomy nor amputation. Their responses included: ‘It is not imagination.’ ‘I have only been sent for consent to amputation.’ ‘Why should I have had so much treatment, if nothing is wrong with my arm?’ Leslie (1988) noted: ‘A pronounced feature was the anger of many of the families about what they saw as the failure of the medical profession to diagnose or to treat their child’s illness properly.’ A typical reaction from a father was: ‘Almost every medical opinion we have had has proved to be wrong’. Leary (2003) found: ‘Refusal by parents to accept the absence of organic disease may be another major stumbling-block to effective management. Such refusal often goes with denial of any domestic tensions or disharmony and with anger directed at medical personnel – attitudes that can greatly hamper the institution of appropriate therapy, as can misguided support for any opposition to treatment expressed by the patient.’

There is not always an angry response to the diagnosis of a PND, but such a reaction is common, and one of the many reasons why plenty of time has to be available to discuss the diagnosis. By dealing calmly with anger, staying logical, and pointing out that the diagnosis of a PND offers hope of a complete cure, and is a far better diagnosis than an aggressive brain tumour or degenerative disease, the storm may gradually settle.

TREATMENT OF PSYCHOCGENIC NEUROLOGICAL DISORDERS

After being told their problems are likely to be the result of stress, combined with suggestions of how to best reduce this, some children and their parents readily accept the diagnosis and the symptoms settle quickly.

Others have prolonged illnesses. These children require psychiatric evaluation, and often admission to hospital. Here the treatment is usually multidisciplinary and may include family therapy, individual psychotherapy, medication for comorbid anxiety and depression, physiotherapy and occupational therapy (Calvert and Jureidini 2003; Koslowska et al. 2012). The stay is usually not short; ‘admissions typically last two weeks’ (Koslowska et al. 2012). Helping these children involves intensive and persistent effort from many people. There is an emphasis on getting the child moving again. For example, the child may be given a programme of walking progressively longer distances each day or two; for example, walk 10 metres on Monday and Tuesday, 25 metres on Wednesday and Thursday, 20 metres twice Friday and Saturday and 50 metres Sunday and Monday (Calvert and Jureidini 2003).

Faust and Soman (2012) highlight the importance of family involvement: ‘family involvement is essential as families must learn the role they play in the treatment plan. Siblings and parents undoubtedly affect the adolescent’s symptoms either by maintaining or exacerbating them. Without significant understanding of psychogenic movement disorders, parents and siblings might be seen as unsupportive and/or as enabling of the adolescent’s condition. Enabling certain anxious or depressive behaviors limit the success of the treatment’.

It is easy to criticise the amount of time and effort and the long hospital stays needed to help some of these children, but many are very ill. Trying to ‘force them’ to get better sooner can result in an escalation of symptoms and an even more prolonged illness. Long admissions are also common in adults with PND. For example, in one study of adults admitted
for the treatment of motor conversion disorder, the median length of admission was 101 days (McCormack et al. 2014).

It seems likely that intensive inpatient programmes work by enabling the child to rest, and get better slowly without loss of dignity, while psychological and family problems are addressed. From the discussion above it can be seen that current inpatient programmes have much in common with previous methods of treatment going back to Chambers in 1861. An interesting part of the programme of Koslowska et al. (2012) involves a limitation of parental visiting hours. These are restricted to 2–3 hours at the end of the day. Koslowska et al. note: ‘We have retained this component of treatment because we have found that when parents remain on the ward at all times, the rehabilitation admissions have not been successful. Part of the reason for this is: the parents’ concern for the child is often expressed in strong non-verbal communications of anxiety, solicitous questions about the child’s symptoms, and caregiving responses to alleviate or manage the symptoms. Unfortunately, these “caring” behaviors often trigger and intensify the child’s symptoms.’

This requirement of reduction of parental contact was the advice given in the past although with greater severity. From Mayer (1899): ‘Unfortunately, it is just in these cases that the parents are unable to treat their children as desired. For this reason, isolation is necessary. The child, brought to a hospital, realizes itself alone; it cannot call on weak parents to act against the injunctions of the physician … Stop all visits, even letters.’ These days such advice would include all electronic devices, representing an even greater deprivation. The view of Hecht (1907) was: ‘When one is denied the intelligent and obedient co-operation of parents, and this is only too often the case, isolation becomes an imperative measure. Isolation to be complete and effective means no visitors, no letters, no messages; in short, no reminders of the past.’

PROGNOSIS

The impression going back to Hecht is that most children with PND do well. Goodyer’s impression (1986) was that: ‘Many of the children appear to be free from psychiatric disturbance and the outcome in terms of the presenting symptoms is generally good, with most of the children at follow-up 1–10 years later free of psychiatric, social or educational difficulties. However, for a small percentage the outcome is poor’. Seventy per cent of 32 children with conversion hysteria reported by Schneider and Rice (1979) required hospital admission for an average of 6 days. While in hospital, 20% had a spontaneous remission of symptoms. Following the initiation of psychiatric treatment, all but one of the inpatients recovered within 3 weeks of the diagnosis being made, including some who had had symptoms for more than 3 years.

In the study of Grattan-Smith et al. (1988), 44% were symptom free at discharge from hospital and another 17% were markedly improved. Leslie (1988) found that ‘Thirteen of the 20 children recovered from their physical symptoms within one month of the start of treatment, and 17 had recovered within three months.’ Ani et al. (2013), found that at one year, of those who could be followed, around 90% showed an improvement in neurological symptoms. In addition, 28% had been diagnosed with a new psychiatric disorder, including anxiety disorder (14%), depressive disorder (13%) and school phobia (9%).

Long-term follow-up studies of children with PND have proven difficult to implement, and although the full picture might not be seen until 30–40 years after presentation, the overall impression is that most do not go on to a lifetime of sickness.

CONCLUSION

Freud compared finding the ‘cause’ of PNDs to the discovery of the source of the Nile, and there is still no widely accepted explanation. As observed in the Lancet (1910) editorial:
‘The literature of hysteria is strewn with the wrecks of theories long since forgotten, as are the very names of their authors’. There are, however, a certain number of findings in PNDs that most would accept. These are: (1) A child has to attain a certain level of maturity, before the illness appears. (2) The vast majority of reports have found PNDs to be more common in females. The exception is during wartime, and in particular in the setting of the trench warfare of World War I, where a large number of young men on both sides were affected by ‘shell shock’. (3) The diagnosis of a PND is based on a careful history and examination. The examination findings are by far the strongest clue to the diagnosis, and the signs have been recognised for more than 100 years. (4) Many different treatment regimes have been used with success. It can be added that current treatment programmes have much in common with the approach recommended by Chambers in 1861.

What remains unresolved, is in the explanation of the ‘apparently voluntary’ signs of a PND. Authorities including Carter, Pager, Janet, Wilson, Walsh and more recently Edwards and Bhatia, have been unable to countenance the possibility that the symptoms could just be ‘deliberately feigned’. Somehow the illness seems to take over the person, and in some it will not let go. Whether this has a ‘neurobiological’ or ‘psychological’ basis, or both contribute, remains an area of uncertainty.

From a practical viewpoint, seeing the signs as a distress signal from a child in a predicament, and attempting to identify and relieve that predicament, provides an approach that allows the child to recover without loss of face and to get back on their feet again, even if, ‘what is really going on’, remains a mystery.

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