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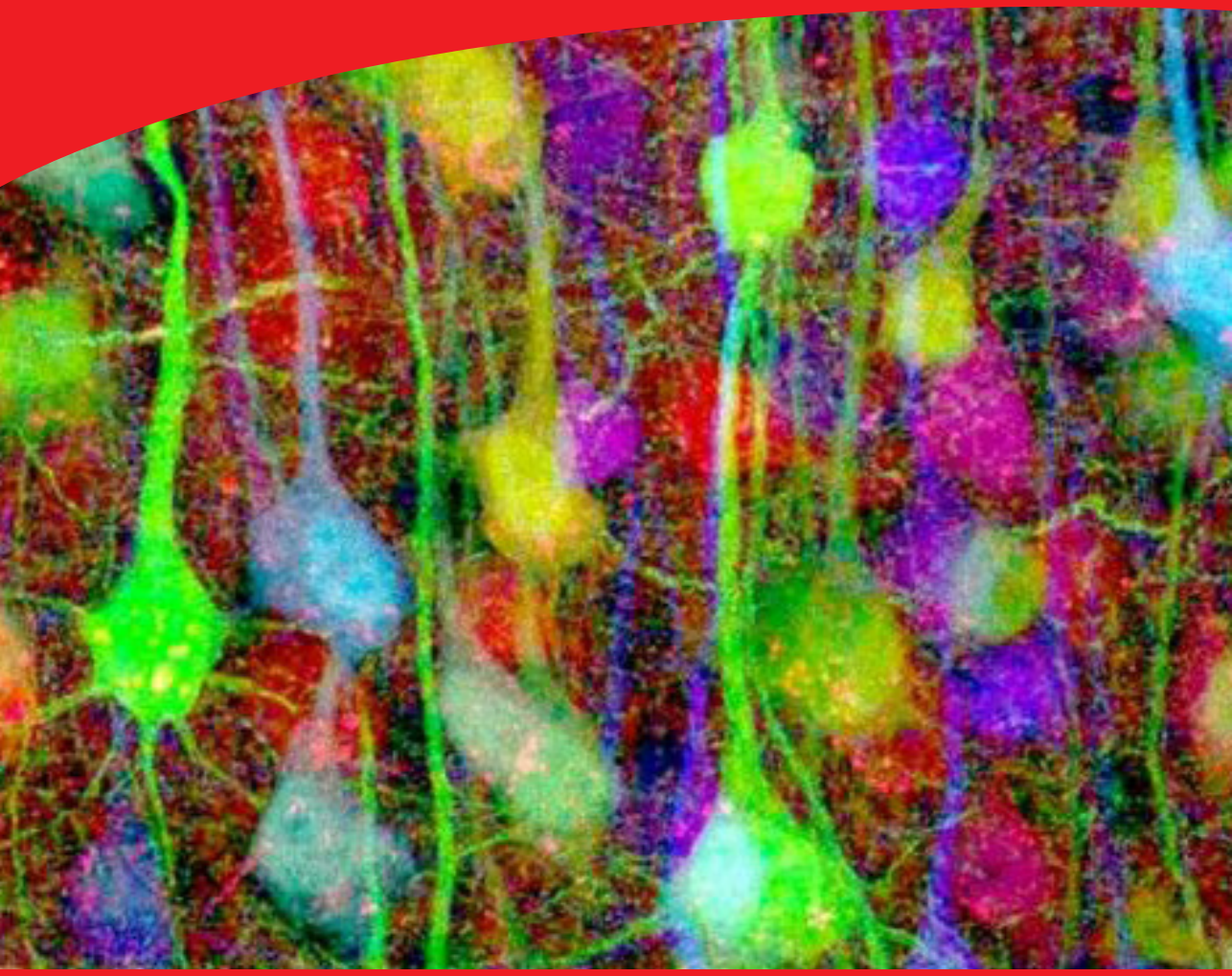
Aicardi's Diseases of the Nervous System in Childhood

4th Edition



Edited by
Alexis Arzimanoglou
with Anne O'Hare, Michael Johnston and Robert Ouvrier

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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 authored or co-authored three internationally recognized books: *Aicardi's Epilepsy in Children*, (Aicardi 1987, 1994; Arzimanoglou, Guerrini, Aicardi 2004) *Diseases of the Nervous System in Childhood*, (Aicardi 1992, 1998, 2009) and *Movement Disorders in Children.* (Fernandez-Alvarez and Aicardi, 2001). He published 259 articles in major international, peer-reviewed journals, and over 100 book chapters.

He was awarded several academic honors and distinctions including the Hower Award of the American Child Neurology 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

Jeanne Couturier and Jean Aicardi, 1958

Jeanne and Jean Aicardi with Giuseppe Erba, Mike Duchowny and his daughter Kate. Miami, Florida, 1995

over the world. His clinical ward rounds will remain unforgettable 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 editorship 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'.

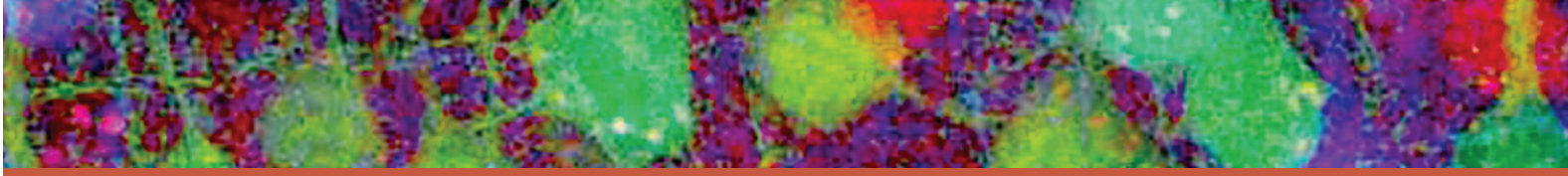
Merci Monsieur!

ALEXIS ARZIMANOGLOU

REFERENCES

1. Arzimanoglou A, Guerrini R, Aicardi J. (2004) *Aicardi's Epilepsy in Children* 3rd edn. London: Lippincott Williams and Wilkins.
2. Aicardi J. (2009) *Diseases of the Nervous System in Childhood.* Clinics in Developmental Medicine. London: Mac Keith Press.
3. Fernandez-Alvarez E, Aicardi J. (2001) *Movement Disorders in Children.* International Review of Child Neurology Series. London: Mac Keith Press.

With Alexis Arzimanoglou, Jaume Campistol-Plana and Emilio Fernandez-Alvarez; Santiago de Compostela, Spain, April 2012.



Jean Aicardi: A Brief Curriculum Vitae

- Born November 8th 1926
- Medical degree, Paris Faculty of Medicine (1955)
- 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
- Honorary Professor of Child Neurology, Institute of Child Health, London, UK (1992–1998)

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

- *Diseases of the Nervous System in Childhood*; Mac Keith Press, 1992, 1998, 2009.
- *Epilepsy in Children.* Lippincott, Williams and Wilkins, 1993
- *Aicardi's Epilepsy in Children* (with A Arzimanoglou, R Guerrini) Lippincott, Williams and Wilkins, 2003
- *Epilepsy. A Comprehensive Textbook,* 2nd edn (with J Engel, TA Pedley, M. Dichter, S. Moshé) Lippincott, Williams and Wilkins, 2007.
- *Movement Disorders in Children* (with E. Fernandez Alvarez) Mac Keith Press, 2001.
- *Epilepsy and Movement Disorders* (with R Guerrini, F Andermann M. Hallett) Cambridge University Press, 2002.
- Founding Editor and Editor-in-Chief, *Epileptic Disorders* (1999–2004)
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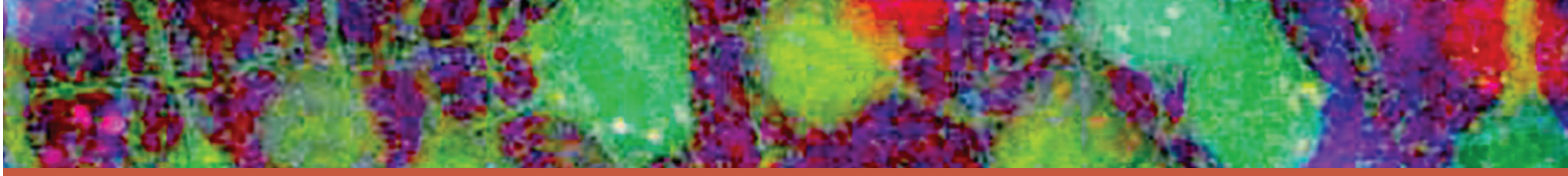


Preface to Third Edition

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 paediatric ailments. Around 20–30% of hospitalized paediatric patients have a neurological problem, either as a sole or as an associated complaint. However, many well-educated paediatricians not infrequently feel uncom-fortable 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 paediatric neurological diseases, whether paediatricians, 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 pre-tend 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 Christopher 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 paediatric 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 'philosophy' of paediatric 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 diagnostic approach. For most conditions, the diagnosis is established 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 necessitates 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 minimize the essentiality of neurological examination, which should be as thorough as possible and largely guided by historical 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 emergence 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 neonatal 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 behavioural problems, which is clearly essential for the diagnosis of the behavioural syndromes that are currently taking a major place in child pathology. Advantage can be taken as often as possible of video-recording for prolonged observation of children's behaviour and is also particularly 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 nervous system is to produce not just reflexes but above all complex 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 prolonged observa-tion of the qualitative aspects of the spontaneous 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 postnatally (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 continuing improvements and new developments such as diffusion-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-orders 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. Investigations should not be performed indiscriminately or systematically 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, sometimes 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

REFERENCES

Cioni G, Mercuri E (2008) *Neurological Assessment in the First Two Years of Life. Clinics in Developmental Medicine No. 176*. London: Mac Keith Press.

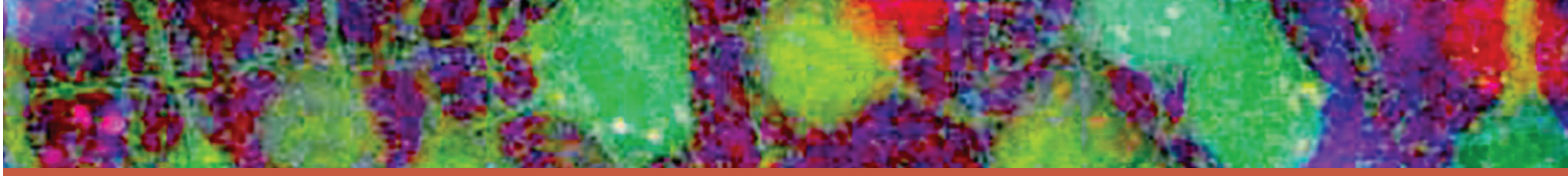
Dooley JM, Gordon KE, Wood EP, et al. (2003) The utility of the physical examination and investigations in the pediatric neurology consultation. *Pediatr Neurol* **28**: 96–9.

Einspieler C, Prechtl HF (2005) Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. *Ment Retard Dev Disabil Res Rev* **11**: 61–7.

Ferrari F, Cioni G, Prechtl HF (1990) Qualitative changes of general move-ments in preterm infants with brain lesions. *Early Hum Dev* **23**: 193–231.

Hill A, Volpe JJ (1989) *Fetal Neurology: International Review of Child Neurology*. Philadelphia: Lippincott, Williams & Wilkins.

Levene MI, Chervenak FA, Whittle M, eds. (2001) *Fetal and Neonatal 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
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March 2018

Acknowledgements

Editors

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.

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MICHAEL JOHNSTON

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CHAPTER 1

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

CHAPTER 4

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CHAPTER 5

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CHAPTER 9

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CHAPTER 10

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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 Neurology Department at the University Hospitals of Lyon, France and the valuable help of our PA Mrs Sophie Naous.

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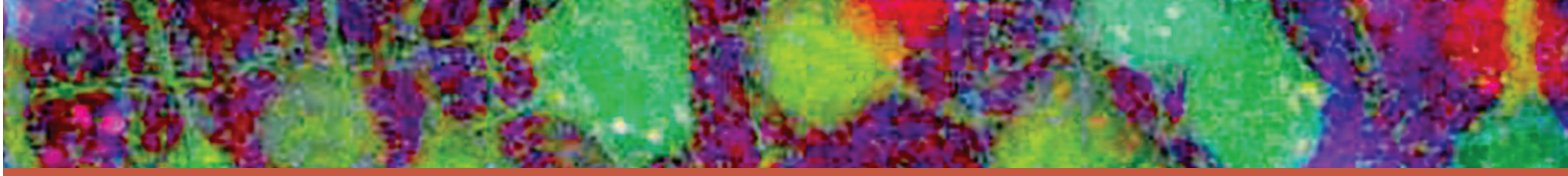

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Fetal and Neonatal Neurology

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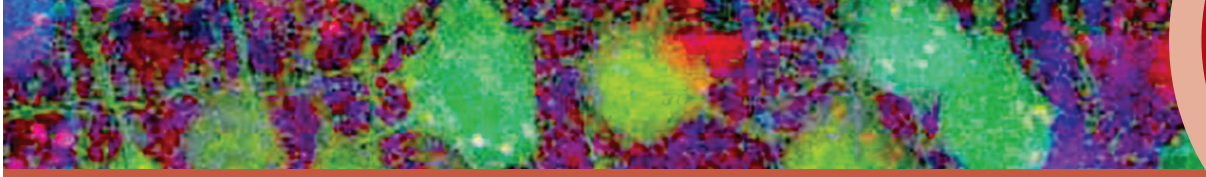

CHAPTER 1

Fetal Neurology

Adré J du Plessis and Michael V Johnston

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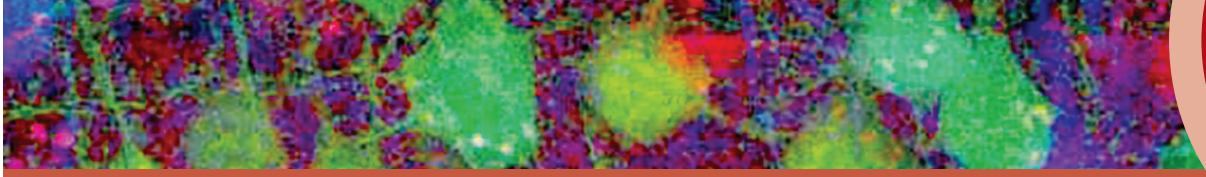

CHAPTER 1

Fetal Neurology

Adré J du Plessis and Michael V Johnston

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 mesenchyme which is interposed between the neural tube and dermal ectoderm. Exposure to the external surface of the neural tube induces the mesenchyme to develop into the vertebral column, meninges and muscle. When the neural tube fails to close exposure to the *internal* ependymal surface of the open central canal 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.

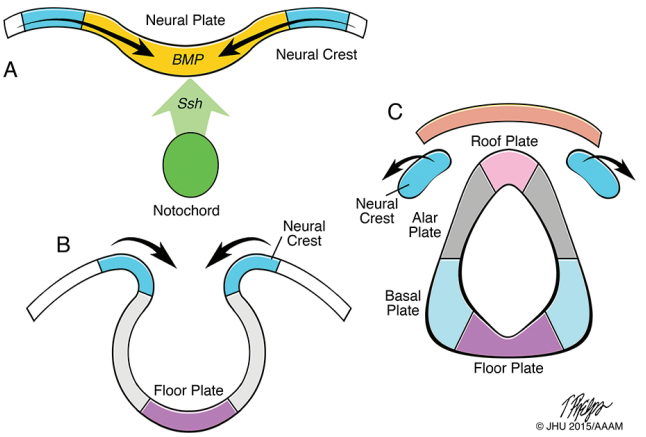

Figure 1.1 **Development of the neural tube and neural crest.** Fig. 1.1a shows the action of dorsalising signals from the ectoderm (e.g. bone morphogenetic proteins; BMP) and ventralising signals (e.g. sonic hedgehog, SHH) from the notochord on the developing neural plate. Fig. 1.1b shows folding of 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.)

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.

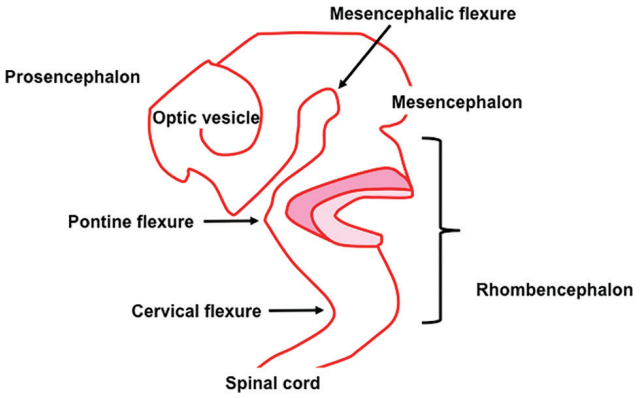

Figure 1.2 **Closure of the anterior neural tube and folding into three vesicles the prosencephalon, mesencephalon, and rhombencephalon**. (Adapted from: Stroustrup Smith et al., 2005.)

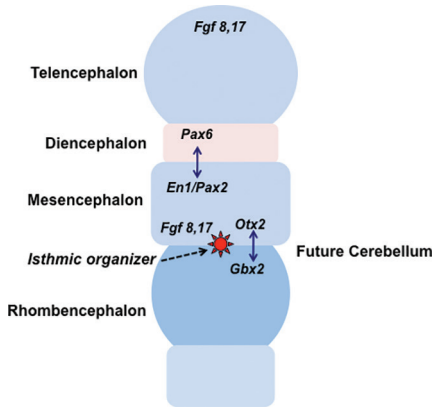

Figure 1.3 Patterning of neural territories in the anterior neural tube by organisers. Diagram showing the definition of the fundamental territories of the anterior neural tube by complex and dynamic effects of suppressor and permissive gene products. Note position of the *isthmic organiser* (IsO) at the mesencephalic-rhombencephalic junction, the location of the cerebellar anlage.

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

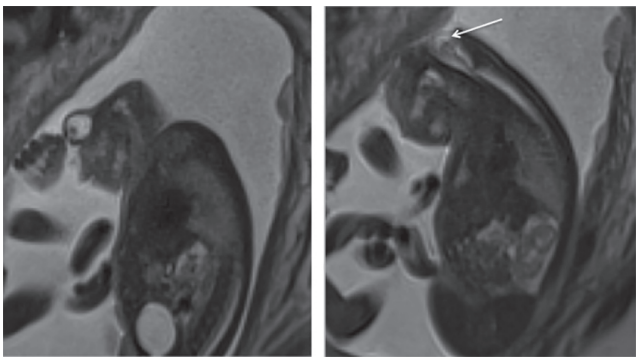

Figure 1.4 **Anencephaly**. Fetal MRI scan showing absence of recognisable neural tissue anterior to the upper brainstem (white arrow).

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

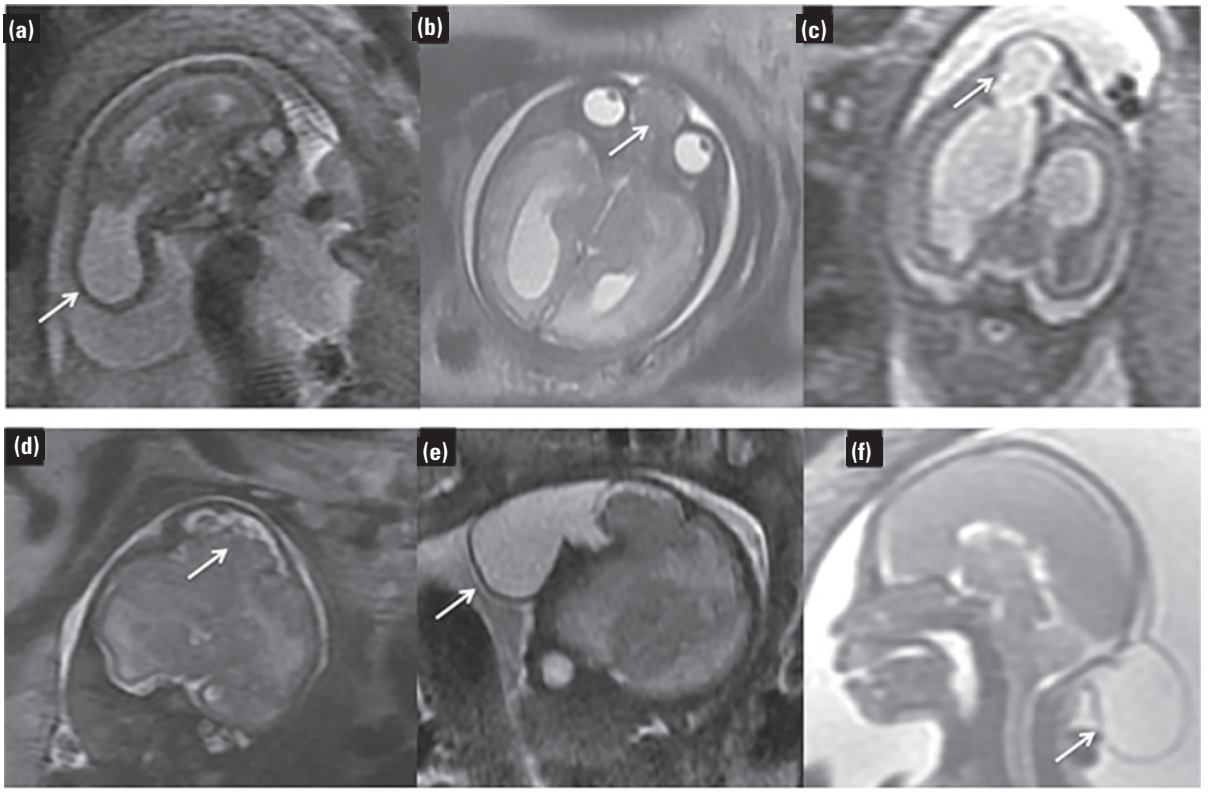

Figure 1.5 **Anterior neural tube defects:** (a) occipital encephalocele; (b) frontal encephalocele; (c) meningoencephalocystocele (with herniation of lateral ventricle); (d–e) frontoparietal calvarial encephalocele; (f) occipital meningocele (no neural elements).

(skin and scalp), with secondary degeneration of the exposed underlying prosencephalic elements.

Encephaloceles

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.

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

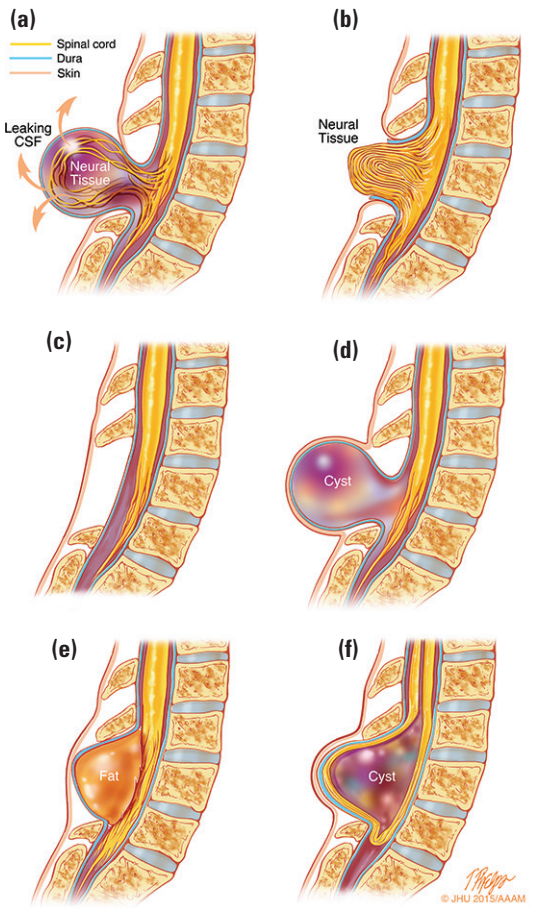

Figure 1.6 **Spina bifida abnormalities** in vertebral arches. Spina bifida refers to a developmental disorder of the spine that leaves a gap in the dorsal bony vertebral arches with or without a gap in the underlying meninges and nervous tissue: (a) and so on to (f) myelomeningocele that includes abnormality in the underlying neural tissue as well as the vertebral arches; (b) myeloschisis that includes abnormalities in spinal nerves; (c) spina bifida occulta which generally spares the neural tissue under the arch; (d) myelocystocele; (e) lipomyelomeningocele; (f) myelocystocele.

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

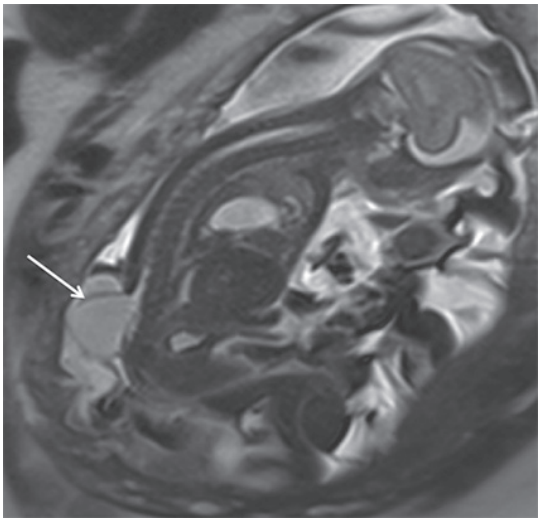

Figure 1.7 Fetal MRI sagittal scan showing lumbosacral **myelomeningocele** (arrow) with tuft of neural tissue entering the CSF-filled cyst.

surface. If the placode is flush with the skin surface the lesion is called a myelocele (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 aetiology 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 (MTFHR) 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

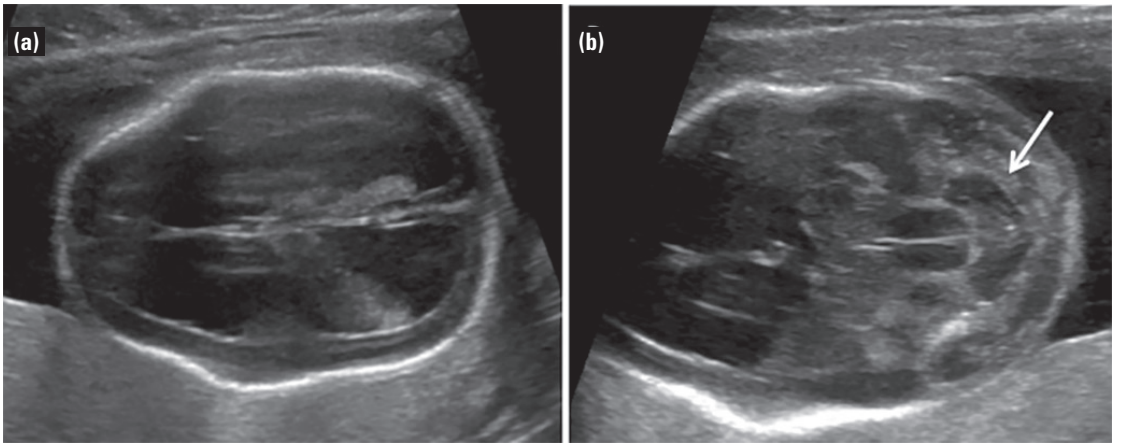

Figure 1.8 (a) Fetal ultrasound showing the **lemon-shaped calvarium** and (b arrow) the **banana-shaped cerebellum** in the crowded posterior fossa.

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 dysaphrism

Prevention should be the primary goal but is complicated by the multifactorial aetiology of open spinal dysaphrism (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 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.

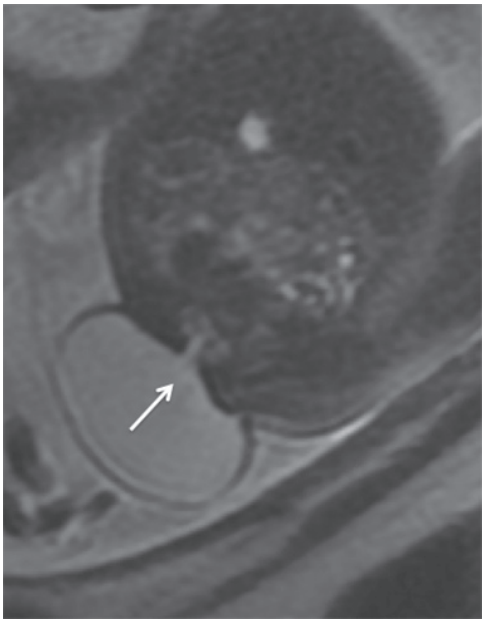

Figure 1.9 Fetal MRI sagittal axial scan showing a **meningocele** without obvious neural tissue in the CSF-filled filled sac, overlying the neural tube defect (arrow).

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 myelocystocele) 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 myelomeningocele.

Spinal lipomas. 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).

Cuadal 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.

Sacrococcygeal 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 events that define the territory of the cerebellar anlagen, (2) development of the fourth ventricular roof and (3) a complex series of proliferative and migratory events that lead to development of the cerebellar hemispheres and vermis. *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 (IsO) 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 IsO 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; Sgaier 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 IsO 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

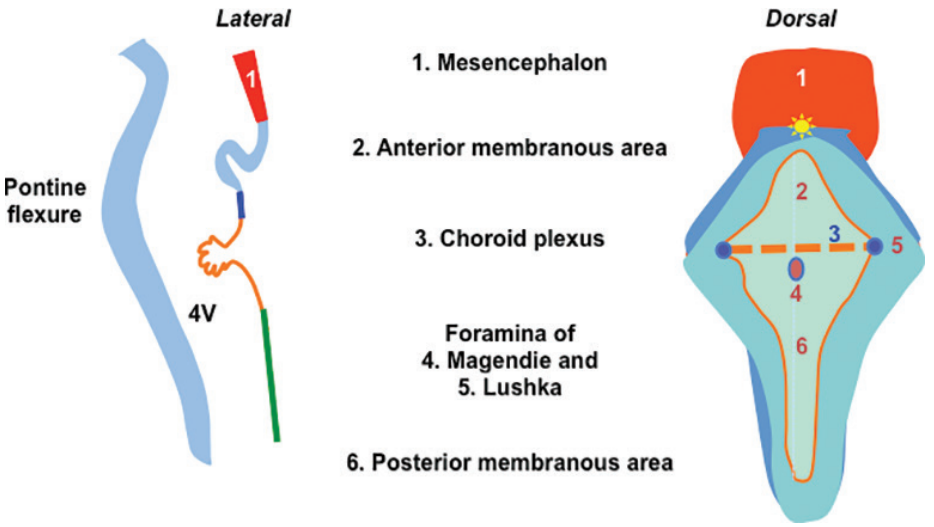

Figure 1.10 **Fourth ventricular roof development**. Diagram showing lateral and dorsal views of the posterior fossa roof. By 10 weeks gestation the fourth ventricular roof is divided into anterior membranous area and posterior membranous area by the developing choroid plexus.

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 **p**osterior fossa anomalies, **h**emangiomata, **a**rterial anomalies, **c**ardiac/aortic anomalies, **e**ye anomalies and **s**ternal 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 choroidea, forms across the fourth ventricle roof, dividing it into the anterior (AMA) and posterior membranous (PMA) areas. The plica choroidea 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 choroidea 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

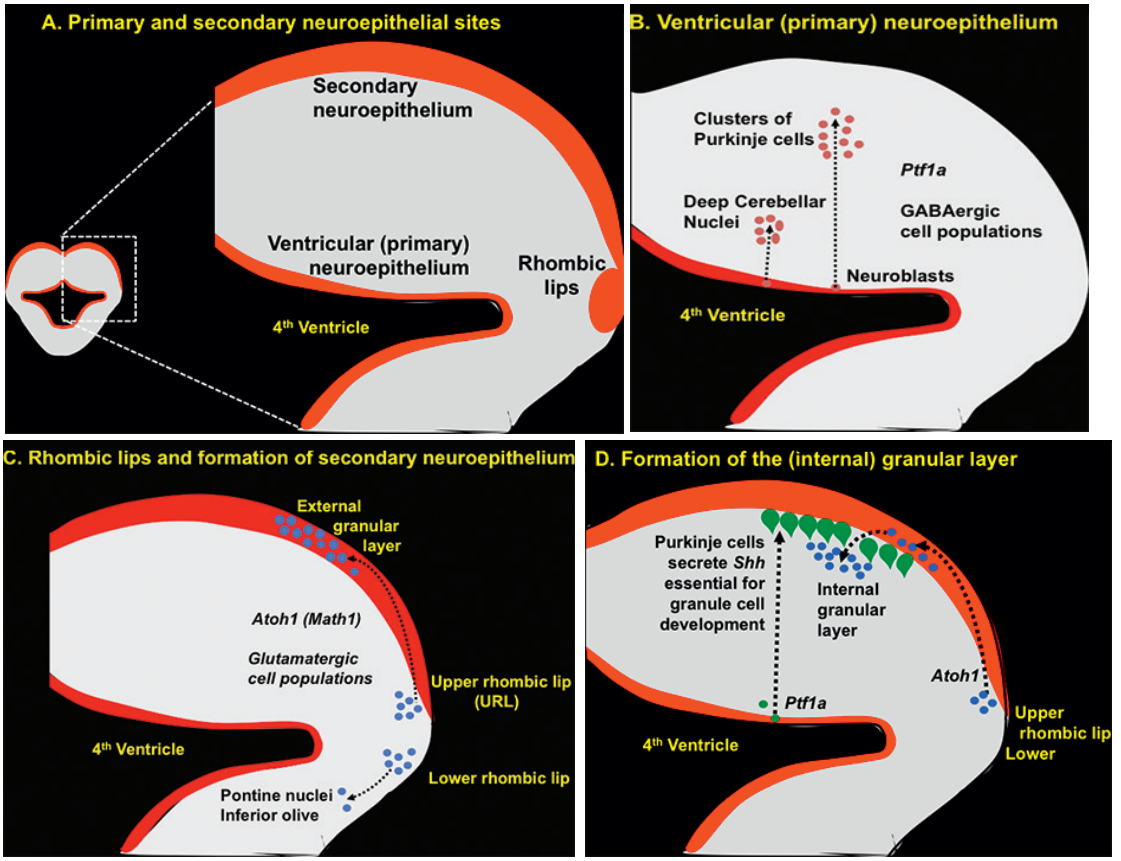

Figure 1.11 (a–d) **Primary and secondary neuroproliferative sites in the developing cerebellum.**

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 germinal 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 fissue 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 hypolasia 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

(such as *Foxc1*) not expressed intrinsically in the developing cerebellum but rather in the overlying mesenchyme. For example, deficient expression of *Foxc1* is known to result in the expression of *Atoh1* in the vermis, with subsequent hypoplasia and abnormal foliation of the vermis (Aldinger et al. 2009). Abnormal *Foxc1* function alone is thought to result in vermian hypoplasia and is likely to play a role in the DWM and mega cisterna magna (Aldinger et al. 2009).

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 at 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).

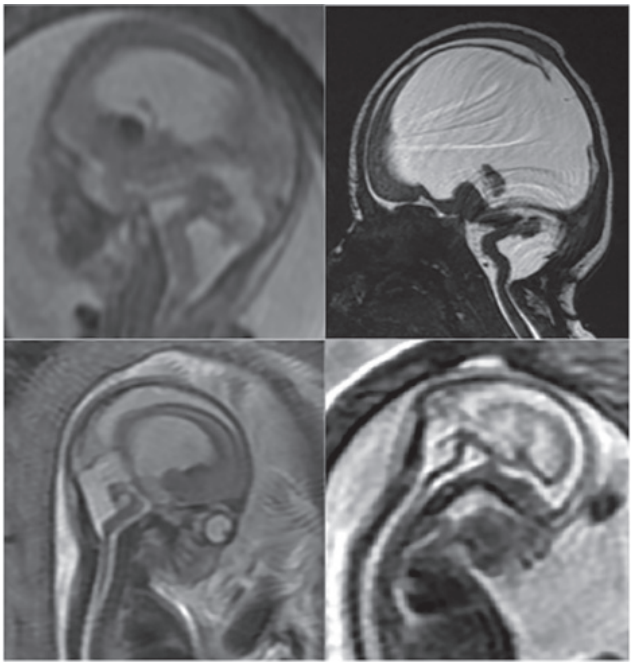

Figure 1.12 Kinked brainstem. Fetal MRI scans showing examples of 'kinked' (z-shaped) brainstem, absent ventral pons, and cerebellar hypoplasia, often associated with other severe cerebral anomalies.

FOXC1 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

Table 1.1 Posterior fossa lesions and excessive fluid

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

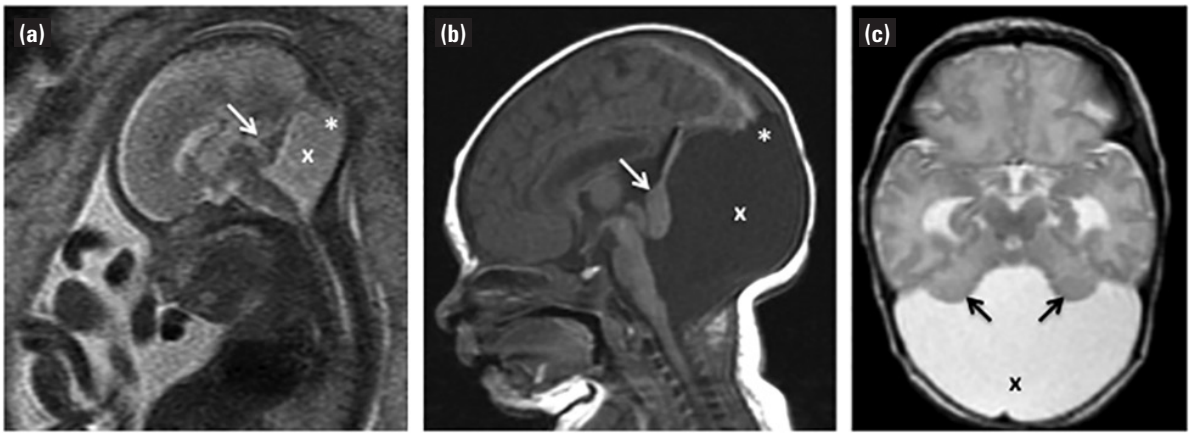

Figure 1.13 Dandy-Walker malformation. (a) Sagittal fetal MRI in a 22-week gestational age fetus. (b) Sagittal and (c) axial MRI in early infancy. *Note*: Elevated torcular Herophili (*); enlarged posterior fossa (x); hypoplastic vermis (white arrow) and hemispheres (black arrows).

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 vermian lobules are present but hypo/dysplastic, 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

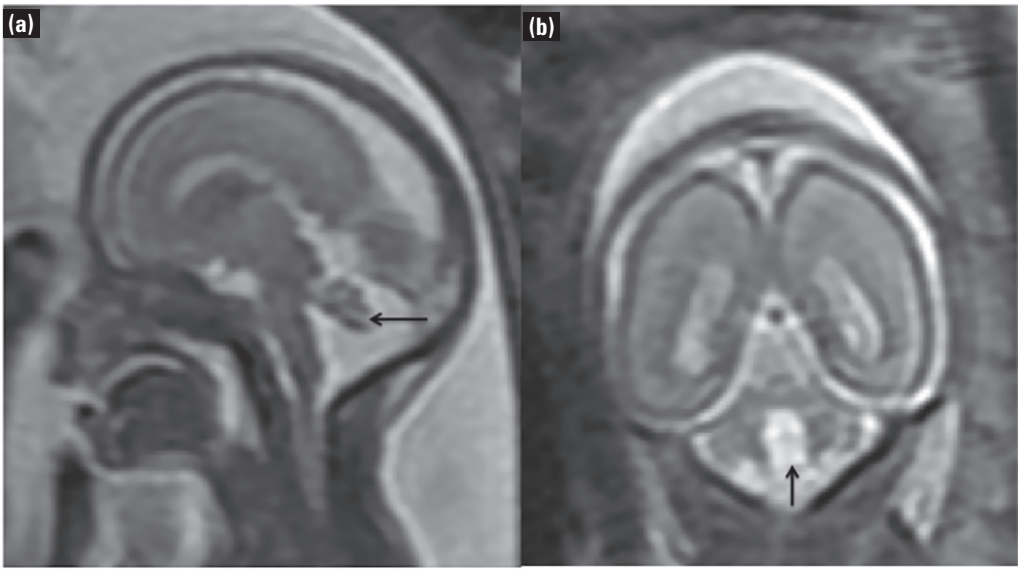

Figure 1.14 (a) Fetal MRI in the sagittal and (b) coronal planes showing inferior **vermian hypoplasia** (arrows).

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 ventriculo-peritoneal 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.

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.

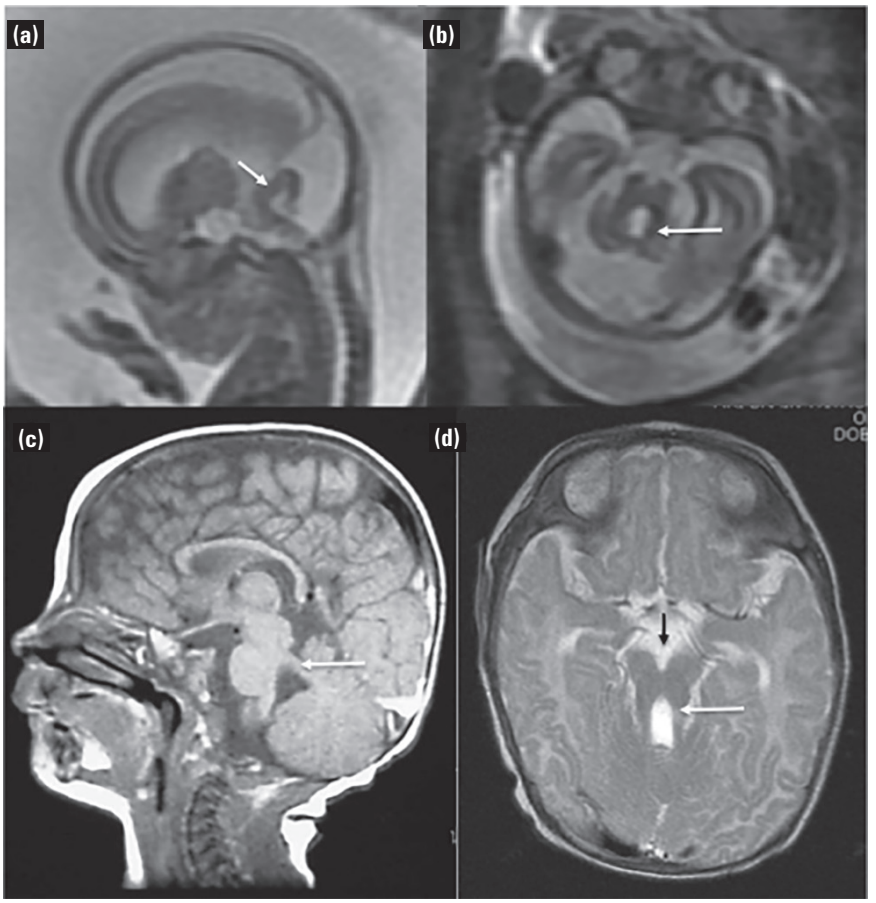

Figure 1.15 Molar tooth sign. MRI studies in the (a,b) fetal and (c,d) postnatal periods in a patient with **Joubert syndrome** showing thick horizontally aligned superior cerebellar peduncle (white arrows in a, c), molar tooth sign (white arrows in b, d) and deep interpeduncular cleft (black arrow in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

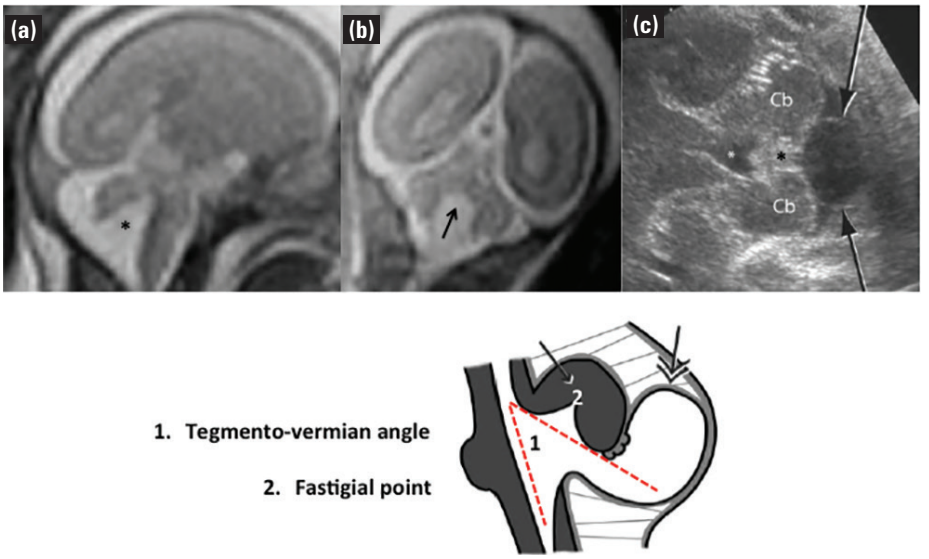

Figure 1.16 Fetal MRI in a 20-week gestation fetus shows a **Blake's pouch cyst**, with an increased tegmento-vermian angle (* in a) and an enlarged fourth ventricle (arrow in b). (c) The mastoid view cranial ultrasound shows the fourth ventricle (white *), normal cerebellar hemispheres (Cb) and vermis (black *) and the walls of the rhombencephalic vesicle (Blake's pouch cyst – black arrows). Adapted from Robinson, and Goldstein (2007).

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.

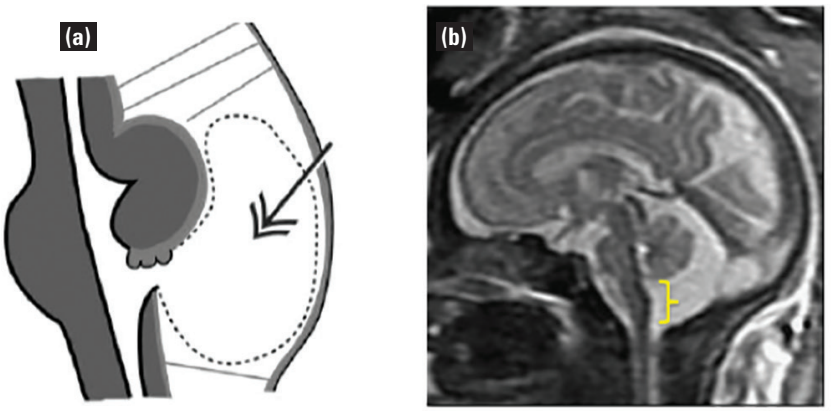

Figure 1.17 (a) Diagram of perforated **Blake's pouch** cyst with tegmento-vermian angle returning to normal but leaving large cisterna magna. (b) **Enlarged cisterna magna** (}) measured as the distance from the inferior vermis border to the foramen magnum. Adapted from Robinson and Goldstein (2007).

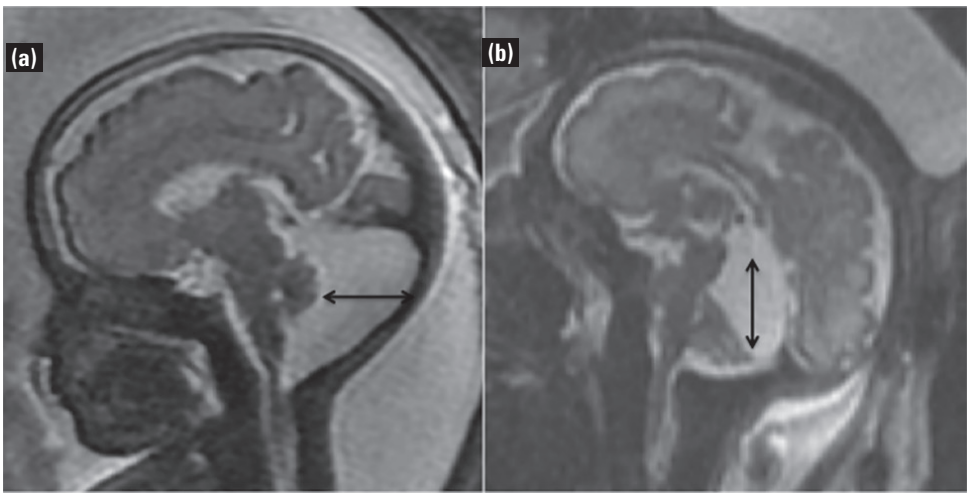

Figure 1.18 **Arachnoid cysts** in the posterior fossa. (a) the cyst (black arrow) is displacing the vermis anteriorly and the fourth ventricle is compressed. (b) the arachnoid cyst (black arrow) is displacing the vermis inferiorly.

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

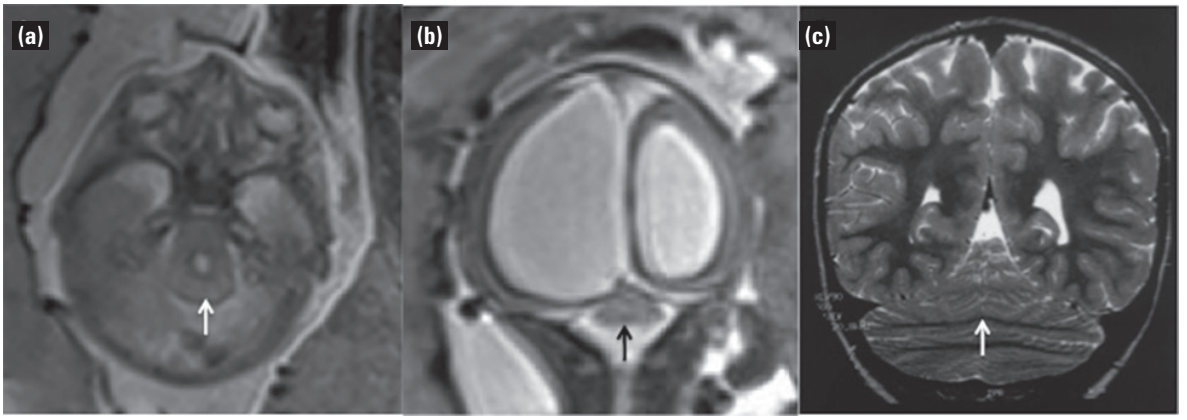

Figure 1.19 **Rhombencephalosynapsis**. (a,b) Fetal MRI studies showing small 'fused' cerebellar hemispheres with no vermis evident (arrows), with associated aqueductal stenosis and severe hydrocephalus; (c) postnatal MRI scan shows with folia and sulci extending across the midline. (Images a, b courtesy Matthew Whitehead, Children's National Medical Center, Washington, DC, USA). Image (c) reproduced from Toelle et al. Rhombencephalosynapsis: Clinical findings and neuroimaging in nine children. *Neuropediatrics 33: 209–14*. © 2002, with permission from Thieme Publishers.

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-occurrrence 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.

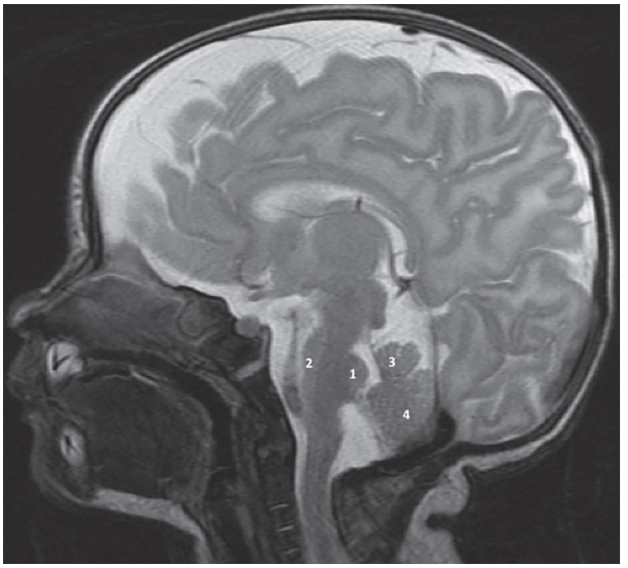

Figure 1.20 **Pontine tegmental cap dysplasia**. Postnatal midline sagittal MRI study showing (1) dorsal tegmental cap; (2) flat ventral pons; (3) small anterior lobe of vermis; and (4) large posterior lobe of vermis.

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

Table 1.3 Pontocerebellar hypoplasia

Pontocerebellar hypoplasia includes a spectrum of degenerative reductions in the volume of the cerebellum and pons in which the cerebellar hemispheres are more affected than the vermis and there is a reduction in the size of the pons. This appearance resembles a dragonfly in which the flattened cerebellar hemispheres represent the wings and preserved vermis represents the body. Supratentorial involvement often includes neocortical atrophy, ventriculomegaly and microcephaly. The most common genes mutated are *TSEN2*, *TSEN34* and *RARS2*.

Type	Gene	Special features
PCH1A	*VRK1*	Spinal muscular atrophy with pontocerebellar hypoplasia
PCH1B	*EXOSC3*	Cerebellar and spinal neuron degeneration
PCH2A	*TSEN54*	Dyskinetic movements and seizures
PCH2B	*TSEN2*	
PCH2C	*TSEN34*	
PCH2E	*VPS53*	Severe intellectual disability
PCH4	*TSEN54*	Severe prenatal form with polyhydramnios, muscle contractures
PCH6	*RARS2*	Neonatal encephalopathy, edema, elevated lactate, mitochondrial respiratory chain defects
PCH8	*CHMP1A*	Severe intellectual delay, hypotonia, spasticity, visual loss
PCH9	*AMPD2*	Microcephaly, seizures, spasticity, brain malformations
PCH10	*CLP1*	Progressive microcephaly, seizures, delayed myelination
	CASK	Severe cerebellar and brainstem hypoplasia with microcephaly and intellectual disability

Namavar et al. (2011) Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. *Brain* **134**: 143–56; Porretti and Boltshauser (2015) Terminology in morphological anomalies of the cerebellum does matter. *Cerebellum and Ataxias* **2**: 8.

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 telecephalon and diencephalon, at around 5 weeks gestation. The telecephalon 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 commisures

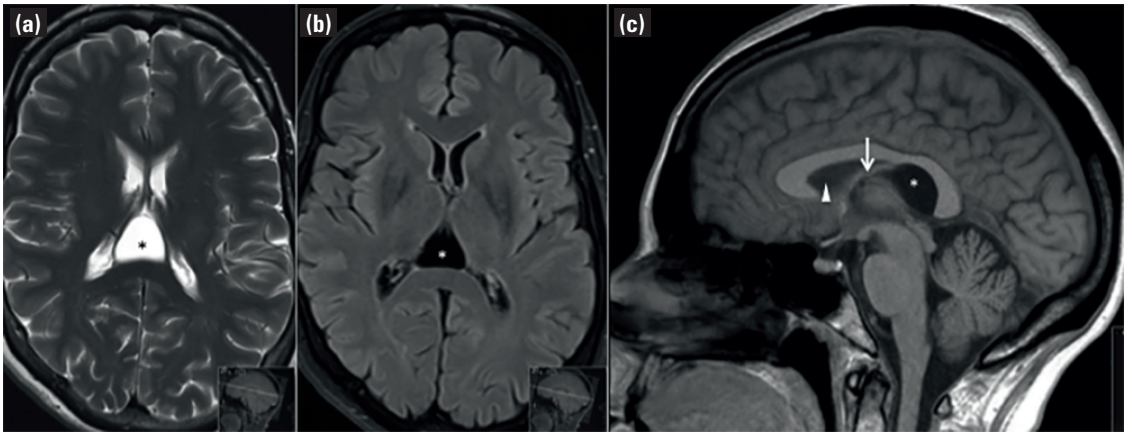

Figure 1.21 (a,b) Postanatal axial and (c) midline sagittal MRI scans with the **cavum velum interpositum** indicated (*). In (c) the white arrow-head indicates the cavum seti pellucidi and the white arrow indicates the fornix. Modified from Radiology MRI (http://radiologymri.blogspot.com/2011/07/cavum-velum-interpositum.html).

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 in 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.

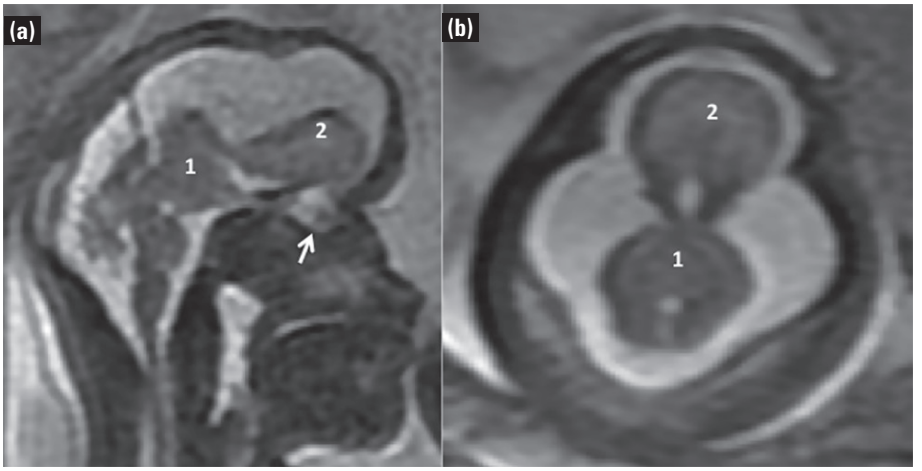

Figure 1.22 Fetal MRI scans (a midline sagittal; b axial) at 22 weeks showing (1) relatively intact brainstem and diencephalon, with (2) only remnants of telecephalon present. Arrow shows midline ocular tissue.

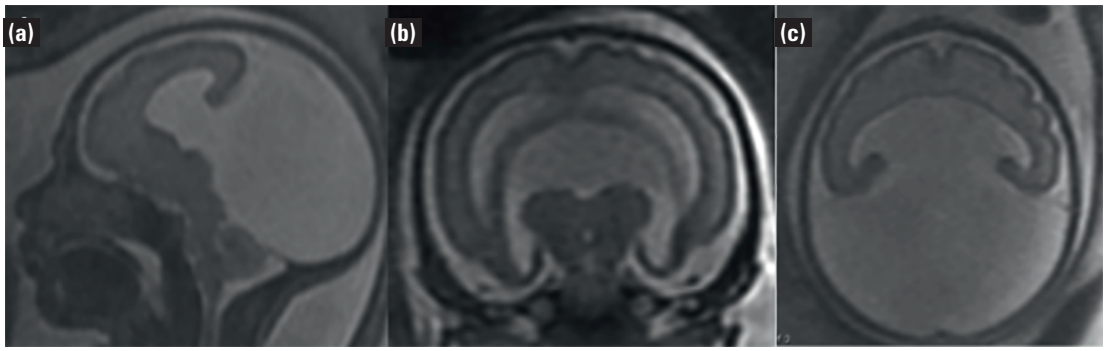

Figure 1.23 Fetal MRI scan showing **alobar holoprosencephaly** (a) large monoventricle, absence of the third ventricle, fusion of the thalamic nuclei, and (b) absence of midline prosencephalic cleavage; (c) shows the horseshoe-shaped monoventricle and large dorsal cyst (a,c).

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). 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 1:10 000 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 frustre 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

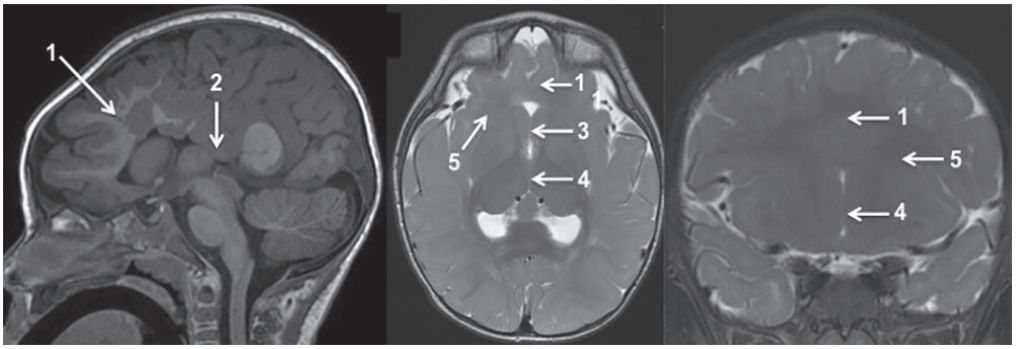

Figure 1.24 Postnatal MRI scan showing **semilobar holoprosencephaly** with (1) failed cleavage of the anterior prosencephalon, (2) absence of anterior corpus callosum, (3) failed cleavage of the caudate nuclei, (4) and thalami and (5) of the frontal horns of the lateral ventricles.

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 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 falx 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 pellucidi may be the only clue (Winter et al. 2010): facial malformations may also be mild or absent.

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.

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. **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 Hebert 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

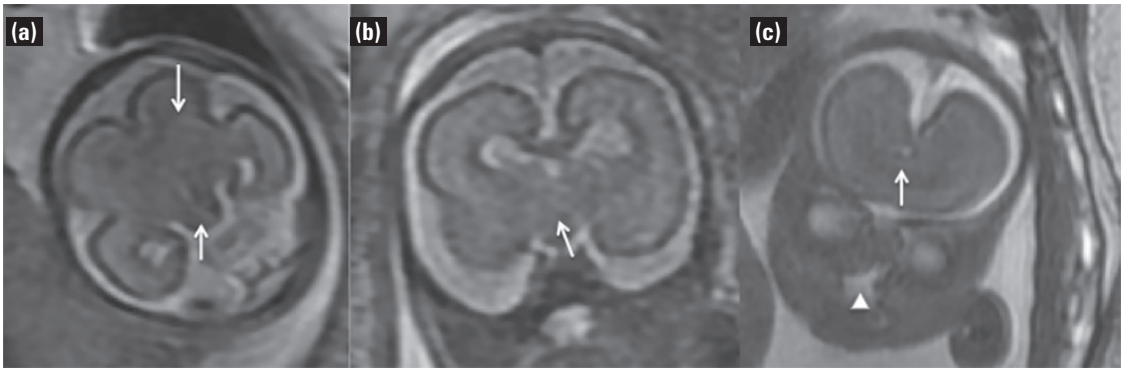

Figure 1.25 **Lobar holoprosencephaly** in a 25-week gestation fetus. Fetal T2-weighted image showing fusion of the ventral forebrain, hypothalamus, and thalamus. (a) absence of the frontal horns of the lateral ventricles (top arrow) and small third ventricle (bottom arrow); (b) diencephalic fusion (solid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

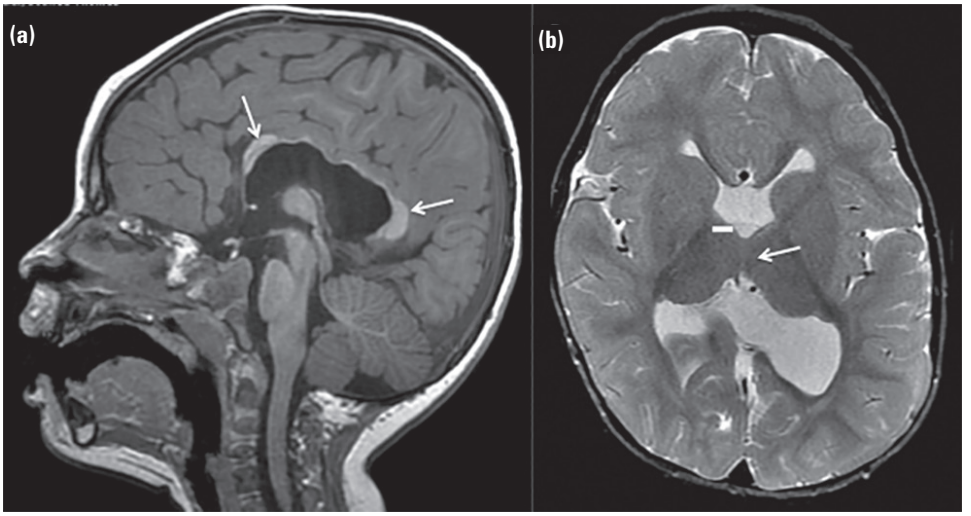

Figure 1.26 Postnatal MRI in an infant with **syntelencephaly**, the midline interhemispheric fusion variant of holoprosencephaly, with failed cleavage of (a) the central frontoparietal region and (b) thalami. The genu and splenium of the corpus callosum are normally formed (a, arrows), but the body is absent.

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 anterverted 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 holopresencephaly are not uniformly lethal. About half of children with alobar HPE die by 5 months but up to one-third of infants survive beyond