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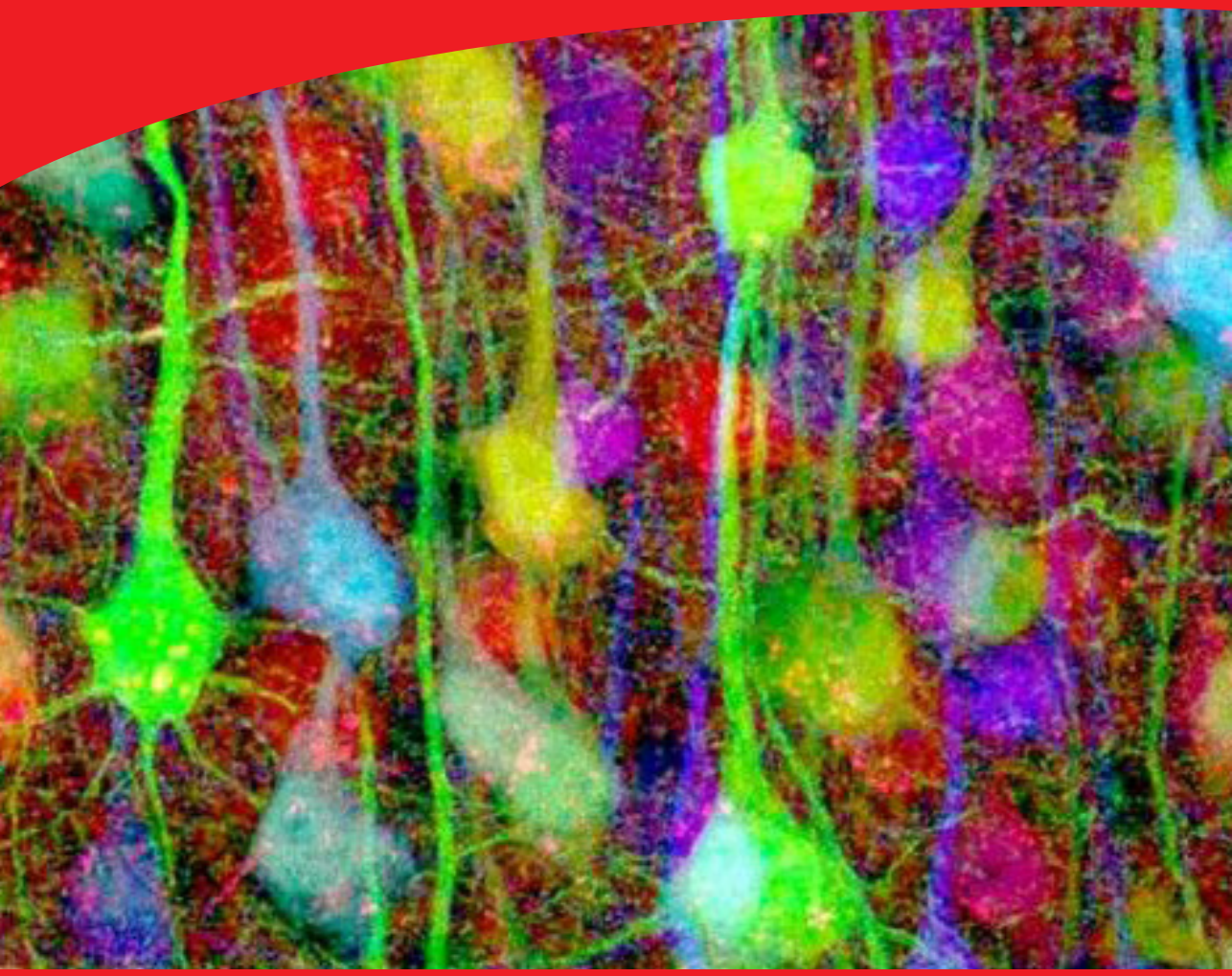
Aicardi's Diseases of the Nervous System in Childhood

4th Edition



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

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Contents

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

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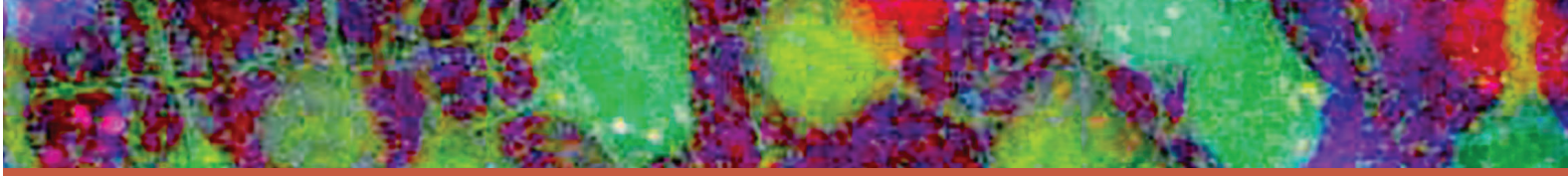
3. Fernandez-Alvarez E, Aicardi J. (2001) *Movement Disorders in Children.* International Review of Child Neurology Series. London: Mac Keith Press.

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)
- 259 articles in international peer-reviewed journals
- 111 book chapters

About the Editors

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

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

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

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

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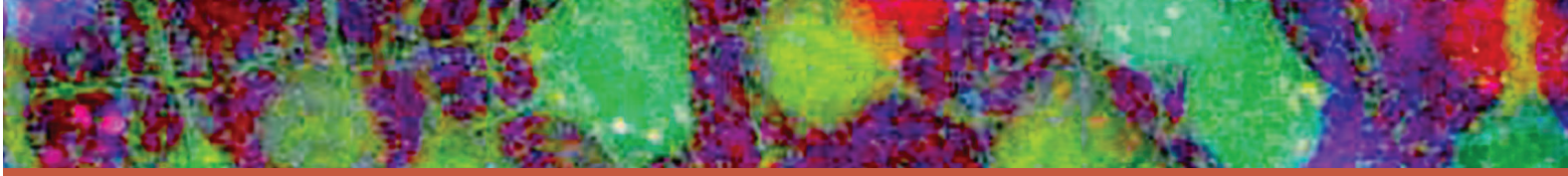

Preface to Third Edition

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

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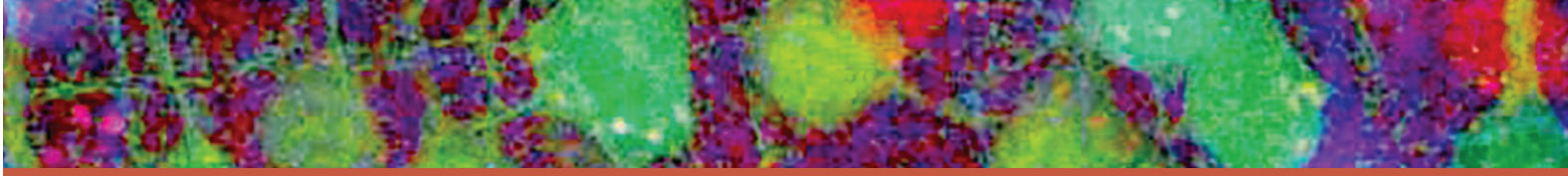

Preface to Fourth Edition

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

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Editors

ALEXIS ARZIMANOGLOU

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Authors

CHAPTER 1

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CHAPTER 12

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CHAPTER 16

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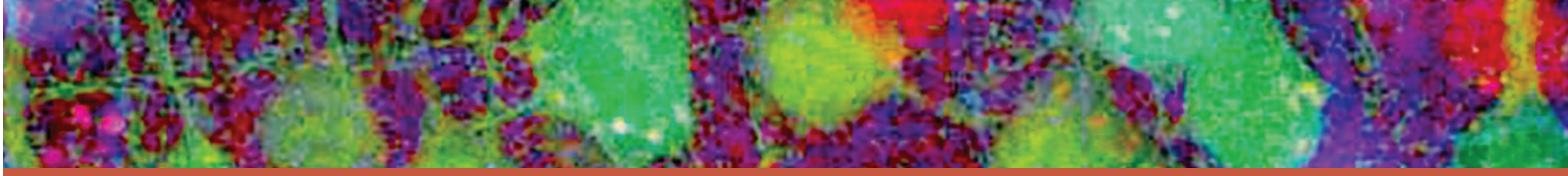
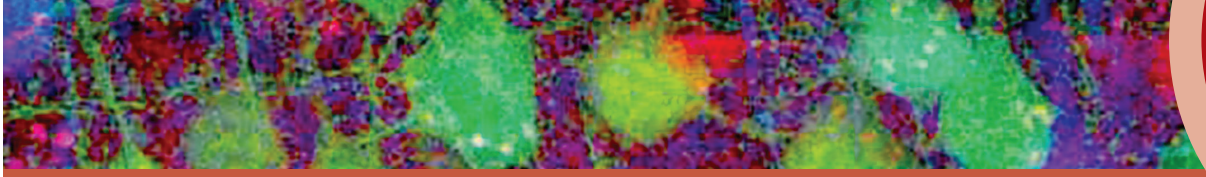


PART I

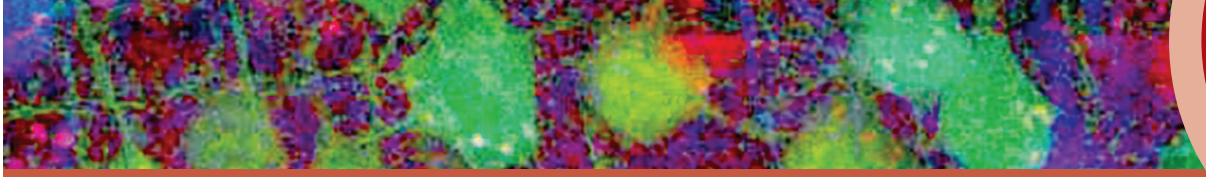
Fetal and Neonatal Neurology



CHAPTER 1

Fetal Neurology

Adré J du Plessis and Michael V Johnston



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.

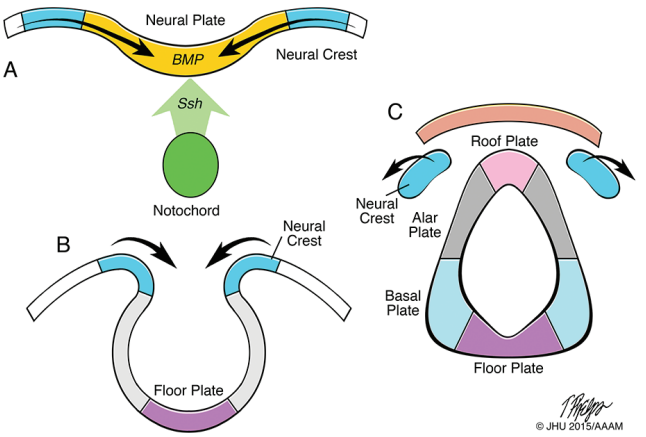


Figure 1.1 **Development of the neural tube and neural crest.** Fig. 1.1a shows the action of dorsalising signals from the ectoderm (e.g. bone morphogenetic proteins; BMP) and ventralising signals (e.g. sonic hedgehog, SHH) from the notochord on the developing neural plate. Fig. 1.1b shows folding of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

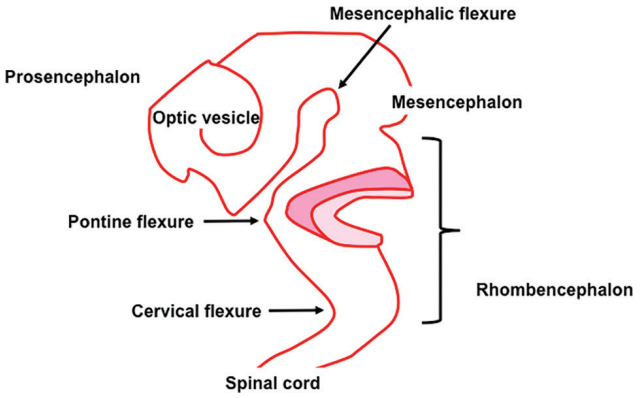


Figure 1.2 **Closure of the anterior neural tube and folding into three vesicles the prosencephalon, mesencephalon, and rhombencephalon**. (Adapted from: Stroustrup Smith et al., 2005.)

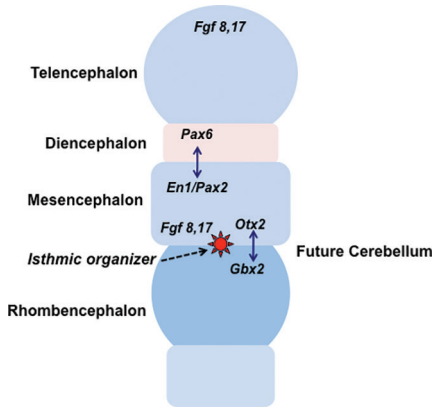


Figure 1.3 Patterning of neural territories in the anterior neural tube by organisers. Diagram showing the definition of the fundamental territories of the anterior neural tube by complex and dynamic effects of suppressor and permissive gene products. Note position of the *isthmic organiser* (IsO) at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

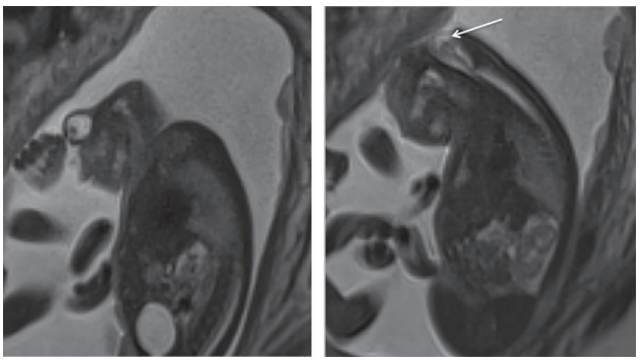


Figure 1.4 **Anencephaly**. Fetal MRI scan showing absence of recognisable neural tissue anterior to the upper brainstem (white arrow).

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

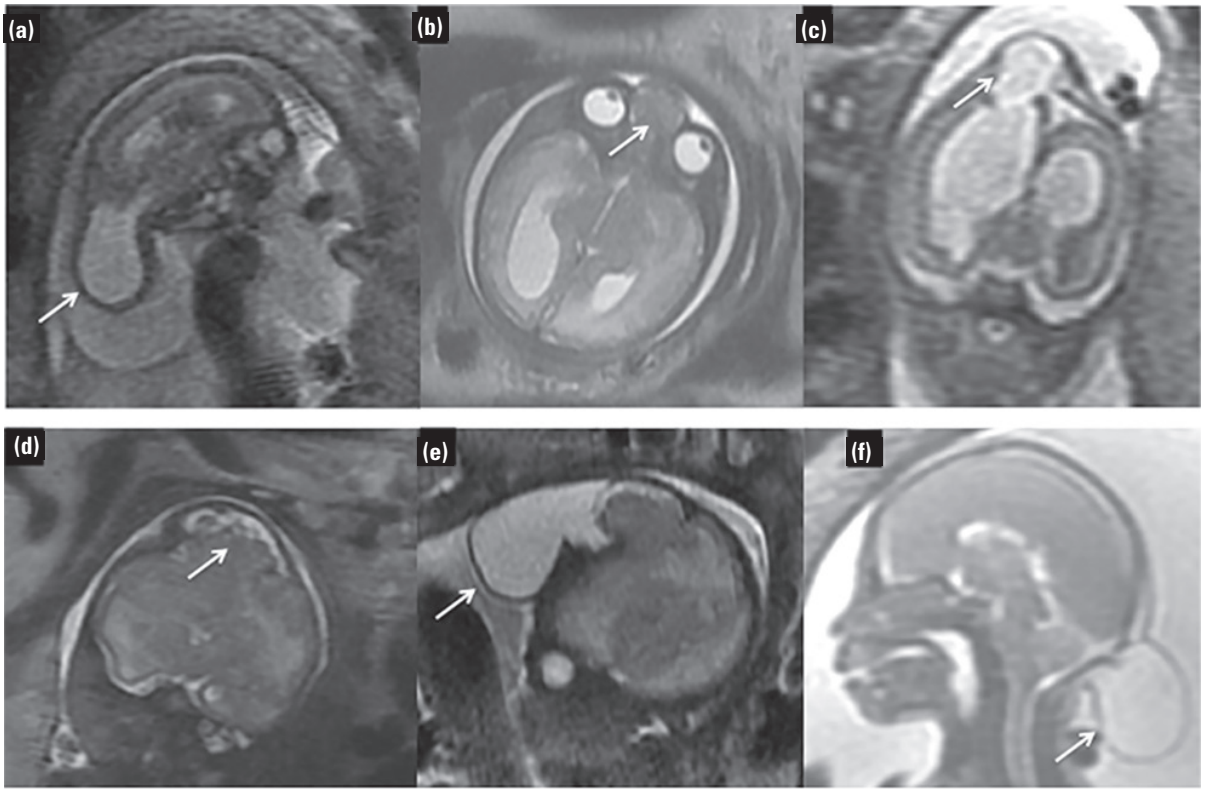


Figure 1.5 **Anterior neural tube defects:** (a) occipital encephalocele; (b) frontal encephalocele; (c) meningoencephalocystocele (with herniation of lateral ventricle); (d–e) frontoparietal calvarial encephalocele; (f) occipital meningocele (no neural elements).

(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

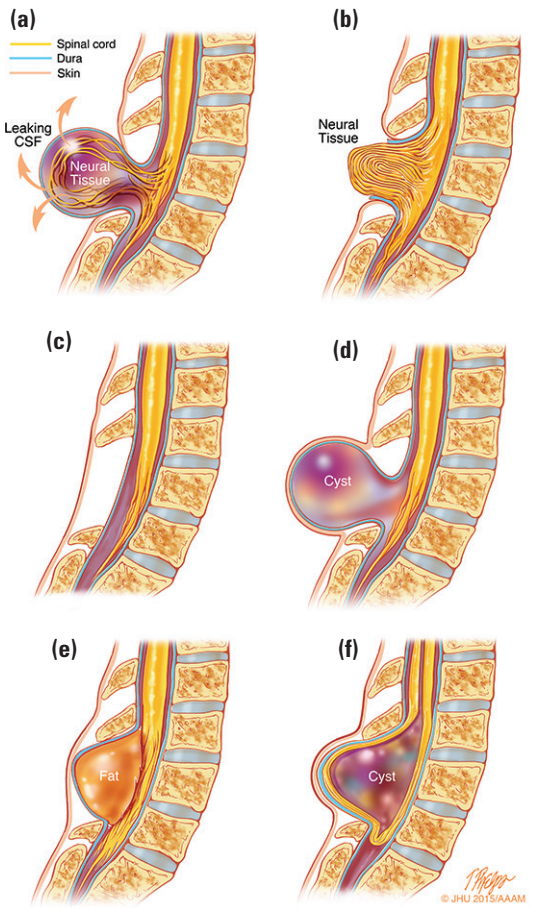


Figure 1.6 **Spina bifida abnormalities** in vertebral arches. Spina bifida refers to a developmental disorder of the spine that leaves a gap in the dorsal bony vertebral arches with or without a gap in the underlying meninges and nervous tissue: (a) and so on to (f) myelomeningocele that includes abnormality 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

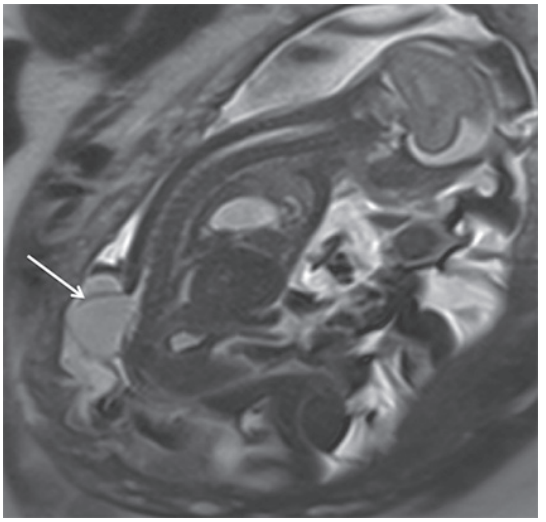


Figure 1.7 Fetal MRI sagittal scan showing lumbosacral **myelomeningocele** (arrow) with tuft of neural tissue entering the CSF-filled cyst.

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